SUPPORTING INFORMATION

Synthesis of chiral nine and twelve-membered cyclic polyamines from natural building blocks

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TABLE OF CONTENTS

GENERAL INFORMATION

All chemicals were used as purchased without further purification if not stated otherwise.

NMR

All NMR experiments were performed at 298 K if not stated otherwise.

NMR experiments at 250 MHz, 400 MHz and 500 MHz were performed on a Bruker Avance III NMR spectrometer equipped with a direct observe 5 mm BBFO smart probe. NMR experiments at 600 MHz were either recorded on a Bruker Avance III NMR spectrometer equipped with a direct observe 5 mm BBFO smart probe or on a Bruker Avance III HD NMR spectrometer equipped with a cryogenic 5 mm four-channel QCI probe (H/C/N/F).

HR-ESI-MS

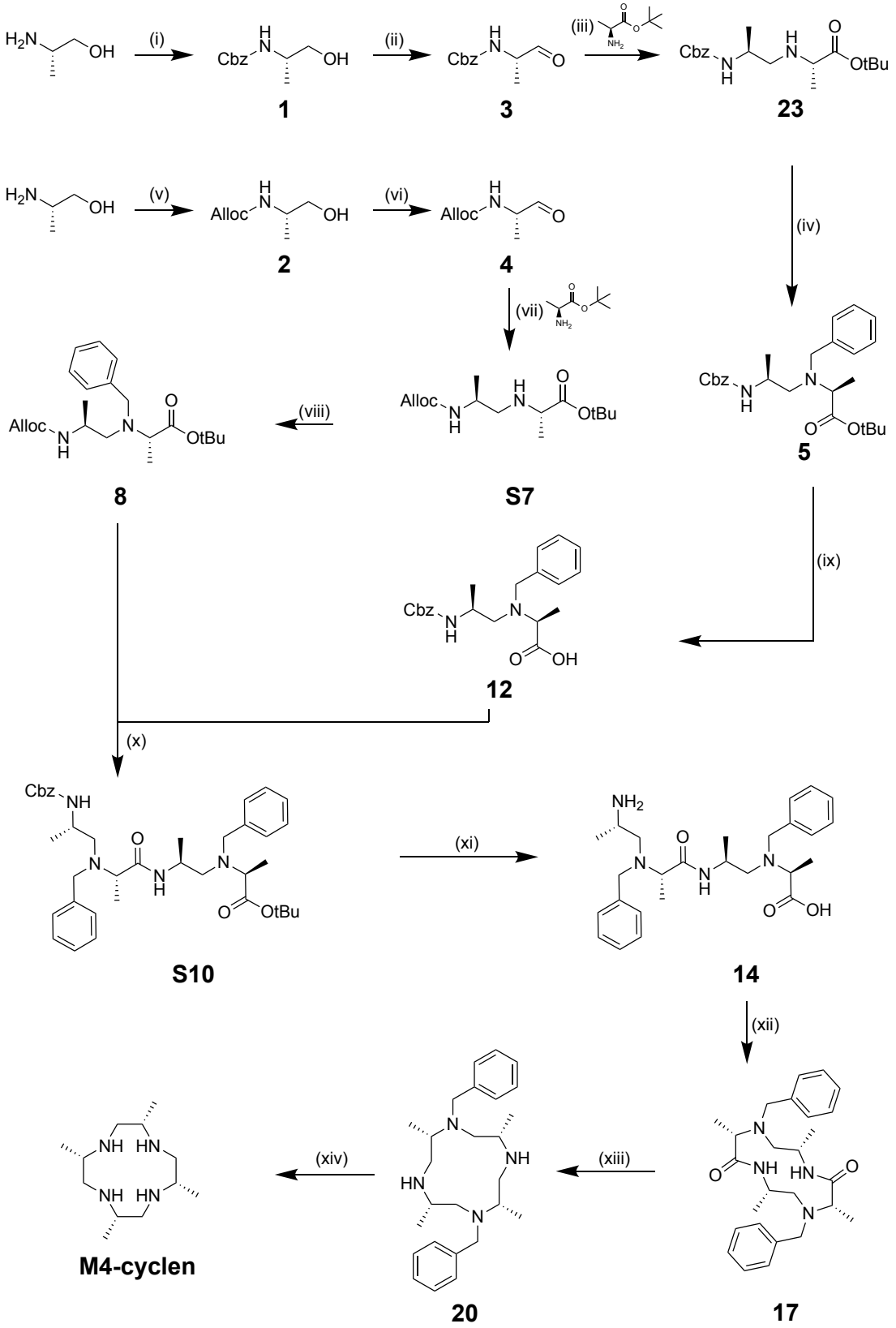
HR-ESI-MS spectra were measured on a Bruker MaXis 4G HiRes ESI Mass Spectrometer using concentrations between 1-10 µg mL^{-1} in methanol or acetonitrile with 0.1% trifluoroacetic acid.

Analytical HPLC-ESI-MS

A Shimadzu LC 20 System equipped with a Shimadzu LCMS-2020 was used. Oven temperature was set to 40 °C.

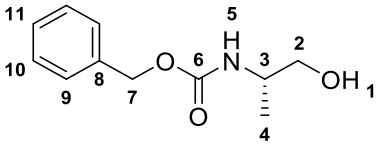
- Column:ReprosilPur120ODS-33µm150x3mm
- Solvent A: Water + 0.1 % TFA
- Solvent B: 90 % Acetonitrile + 10 % water + 0.085 % TFA.
- Flow rate: 1.0 ml/min
- UV Detector: set to 254 and 280 nm
- Gradient: 2 minutes at 5 % B followed by a gradient over 4 min from 5 % B to 100 % B. These conditions were kept for 8 min followed by a gradient from 100 % B to 5 % B over 1 min. These conditions were kept constant for another 7 min.
- ESI-MS: positive mode 100-1500 m/z.

SYNTHESIS OF M4-CYCLEN



Scheme S1: Synthetic route towards M4-cyclen. Reaction conditions: i) Cbz-Cl, Na_2CO_3, H_2O, EtOAc, 20-25 °C, 1 h; ii) IBX, DMSO, EtOAc, RF, 3.5 h; iii) $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 16 h; iv) BnBr, K_2CO_3, MeCN, 50 °C, 16 h; v) Alloc-Cl, Na_2CO_3, H_2O, EtOAc, 20-25 °C, 1 h; vi) IBX, DMSO, EtOAc, RF, 5 h; vii) $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 1 h; viii) BnBr, K_2CO_3, MeCN, 40 °C, 8 h; ix) HCl in dioxane, 40 °C, 18 h; x) PhSiH, $Pd(PPh_3)_4$, HATU, DIPEA, 20-25 °C, 4 h; xi) HBr in AcOH 16 wt. %, 40 °C, 30 min; xii) HATU, DIPEA, MeCN, 20-25 °C, 20 min; xiii) TMS-Cl, $LiAlH_4$, THF/CH_2Cl_2, 0-5 °C → 20-25 °C; xiv.) ammonium formate, Pd/C, EtOH, RF, 16 h.

Benzyl (*S*)-(1-hydroxypropan-2-yl)carbamate (1).



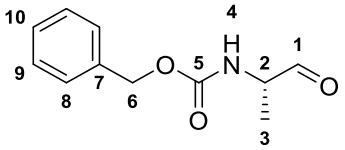
Sodium carbonate (245.0 g, 2.32 mol, 3.05 eq.) was dissolved in water (500 mL). A solution of *(S)*-alaninol (57.0 g, 0.76 mol, 1.00 eq.) in ethyl acetate (180 mL) was added at 20-25 °C. The biphasic mixture was stirred vigorously and benzyl chloroformate (133.0 g, 0.78 mol, 1.03 eq.) was added at 20-25 °C. After addition, the biphasic mixture was stirred for 1 h and then diluted with water (500 mL) and ethyl acetate (600 mL). The so formed clear layers were separated and the aqueous layer was extracted with ethyl acetate (250 mL). The combined organic layers were washed with water (250 mL), dried over sodium sulphate and evaporated to dryness. The crude product was recrystallized from ethyl acetate / cyclohexane and benzyl (*S*)-(1-hydroxypropan-2-yl)carbamate was obtained as a white solid (149.0 g, 0.71 mol, 93.8%).

HR-ESI-MS: calcd. for $[M+Na]^+$ $C_{11}H_{15}NNaO_3$ m/z=232.0944, found m/z=232.0944.

^{1}H-NMR (600.13 MHz, 298K, $CDCl_3$): δ= 7.41-7.28 (m, 5H, H-9, H-10, H-11), 5.10 (d, ^2J=12.1 Hz, 1H, H-7a), 5.07 (d, ^2J=12.1 Hz, 1H, H-7b), 5.06 (bs, 1H, H-5), 3.82 (ddd,^3J=6.8 Hz, ^3J=5.6 Hz, ^3J=2.4 Hz, 1H, H-3), 3.63 (dd, ^2J=10.2 Hz, ^3J=2.4 Hz, 1H, H-2a), 3.50 (dd, ^2J=10.2 Hz, ^3J=5.6 Hz, 1H, H-2b), 2.73 (bs, 1H, H-1), 1.15 (d, ^3J=6.8 Hz, 3H, H-4).

^{13}C-NMR (150.9 MHz, 298K, $CDCl_3$): δ= 156.70 (C-6), 136.46 (C-8), 128.64 (C-10), 128.27 (C-11), 128.23 (C-9), 66.93 (C-7), 66.83 (C-2), 49.05 (C-3), 17.32 (C-4).

Benzyl (*S*)-(1-oxopropan-2-yl)carbamate (3).



(*S*)-(1-hydroxypropan-2-yl)carbamate (**1**) (45.0 g, 0.22 mol, 1.0 eq.) , 2-iodoxybenzoic acid (IBX) (90.3 g, 0.32 mol, 1.5 eq.) were suspended in ethyl acetate (450 mL). The suspension was heated to reflux. At reflux dimethyl sulfoxide (45.8 mL, 0.65 mol, 3.0 eq.) was added. The suspension was further refluxed for 3.5 h before cooled down to 0-5 °C. The suspension was filtered and washed with ethyl acetate (150 mL). The filtrate was extracted with aqueous saturated sodium hydrogen carbonate (450 mL), water (450 mL) and brine (300 mL). The organic layer was dried over sodium sulphate and evaporated to dryness yielding a colourless oil (41.5 g, 0.20 mol, 93.2%).

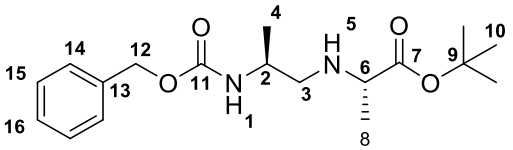
HR-ESI-MS: calcd. for $[M+H]^+$ $C_{11}H_{14}NO_3$ m/z=208.0968, found m/z=208.0967.

^{1}H-NMR (250.13 MHz, 298K, CD_3CN): δ= 9.51 (d, ^{3}J=0.5 Hz, 1H, H-1), 7.54-7.11 (m, 5H, H-8, H-9, H-10), 5.10 (s, 2H, H-6), 4.08 (qdd, ^{3}J=7.4 Hz, ^{3}J=7.0 Hz, ^{3}J=0.5 Hz, 1H, H-2), 1.27 (d, ^{3}J=7.4 Hz, 3H, H-3).

^{13}C-NMR (125.8 MHz, 298K, $CDCl_3$): δ= 198.97 (C-1), 155.82 (C-5), 136.15 (C-7), 128.59 (C-9), 128.29 (C-10), 128.17 (C-8), 67.09 (C-6), 55.93 (C-2), 14.86 (C-3).

HPLC: A sample of the product was dissolved in ethanol and reduced using excess sodium borohydride. After aqueous work-up the crude product was purified by flash column chromatography and subjected to chiral HPLC analysis. The e.r. of > 99:1 was determined by HPLC using a *Chiralpakl* AD-H analytical column (1.0 mL/min, isopropanol/heptane, 10:90): (S_a) t_R= 8.7 min (R_a) t_R= 11.3 min; racemic reference material was obtained starting from *DL*-alaninol.

***tert*-Butyl ((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-alaninate (23).**



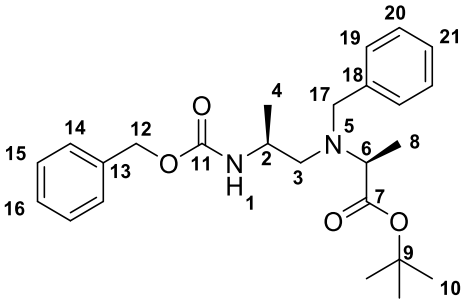
Benzyl (*S*)-(1-oxopropan-2-yl)carbamate (**3**) (41.4 g, 0.20 mol, 1.0 eq.) was dissolved in dichloromethane (600 mL). To this solution *L*-alanine tert-butyl ester (30.6 g, 0.20 mol, 1.0 eq.) was added. The solution was stirred at 20-25 °C for 5 min. followed by the addition of sodium triacetoxyborohydride (141.0 g, 0.60 mol, 3.0 eq.). The reaction mixture was stirred at 20-25 °C for 16 h. The excess of sodium triacetoxyborohydride was quenched with aqueous saturated sodium hydrogen carbonate (450 mL) and the pH adjusted to >9 by addition of triethylamine (100 mL). The two layers were separated, and the organic layer was washed with water (250 mL) and dried over sodium sulphate. The organic layer was evaporated to dryness yielding a colourless oil that slowly crystal-lised forming a white solid (66.0 g, 0.196 mol, 98.1%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{18}H_{29}N_2O_4$ m/z=337.2122, found m/z=337.2121.

^{1}H-NMR (600.13 MHz, 298K, DMSO-d_6): δ= 7.38-7.33 (m, 3H, H-15, H-16), 7.32-7.28 (m, 2H, H-14), 7.09 (d, ^{3}J=8.1 Hz, 1H, H-1), 5.01 (d, ^{2}J=12.8 Hz, 1H, H-12a), 4.98 (d, ^{2}J=12.8 Hz, 1H, H-12b), 3.54 (dddq, ^{3}J=8.1 Hz, ^{3}J=6.3 Hz, ^{3}J=6.2 Hz, ^{3}J=6.6 Hz, 1H, H-2), 3.09 (q, ^{3}J=6.9 Hz, 1H, H-6), 2.47 (dd, ^{2}J=11.5 Hz, ^{3}J=6.2 Hz, 1H, H-3a), 2.40 (dd, ^{2}J=11.5 Hz, ^{3}J=6.3 Hz, 1H, H-3b), 1.86 (bs, 1H, H-5), 1.40 (s, 9H, H-10), 1.11 (d, ^{3}J=6.9 Hz, 3H, H-8), 1.03 (d, ^{3}J=6.6 Hz, 3H, H-4).

^{13}C-NMR (150.9 MHz, 298K, DMSO-d_6): δ= 174.46 (C-7), 155.53 (C-11), 137.25 (C-13), 128.31 (C-15), 127.72 (3C, C-14, C16), 79.91 (C-9), 65.03 (C-12), 56.67 (C-6), 52.18 (C-3), 46.61 (C-2), 27.69 (C-10), 18.66 (C-8), 18.58 (C-4).

***tert*-Butyl-*N*-Benzyl-*N*-((*S*)-2 (((Benzylox)carbonyl)amino)propyl)-*L*-alaninate (5).**



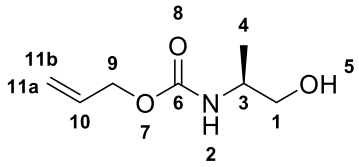
tert-Butyl ((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-alaninate (**23**) (23.7 g, 70.4 mmol, 1.0 eq.) was dissolved in acetonitrile (200 mL) and potassium carbonate (10.7 g, 77.4 mmol, 1.1 eq.) was added. To this suspension benzyl bromide (12.6 g, 73.9 mmol, 1.05 eq.) was added and the reaction mixture was stirred at 50 °C for 16 h. Excess of benzyl bromide was quenched with triethylamine (15 mL). The reaction mixture was then cooled to 20-25 °C filtered and evaporated to dryness yielding a crude yellow oil. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate / cyclohexane (7:3)) yielding a yellowish oil (25.3 g, 59.3 mmol, 84.2%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{25}H_{35}N_2O_4$ m/z= 427.2591, found m/z= 427.2596.

^{1}H-NMR (600.13 MHz, 298K, CD_3CN): δ= 7.41-7.17 (m, 10H, H-14, H-15, H-16, H-19, H-20, H-21), 5.81 (bs, 1H, H-1), 5.06 (d, ^2J=12.6 Hz, 1 H, H-12a), 5.01 (d, ^2J=12.6 Hz, 1H, H-12b), 3.76 (d, ^2J=14.2 Hz, 1 H, H-17a), 3.71 (d, ^2J=14.2 Hz, 1H, H-17b), 3.59 (m, 1H, H-2), 3.28 (q, ^3J=7.1Hz, 1H, H-6), 2.58 (dd, ^2J=13.4 Hz, ^3J=8.1 Hz, 1H, H-3a), 2.52 (dd, ^2J=13.4 Hz, ^3J=6.3 Hz, 1H, H-3b), 1.44 (s, 9H, H-10), 1.17 (d, ^3J=7.1 Hz, 3H, H-8), 1.09 (d, ^3J=6.3 Hz, 3H, H-4).

^{13}C-NMR (100.61MHz, 298K, CD_3CN): δ= 174.1 (C-7), 156.97 (C-11), 141.1 (C-18), 138.6 (C-13), 129.5 (C-arom.), 129.4 (C-arom.), 129.2 (C-arom.), 128.8 (C-19), 128.7 (C-14), 127.9 (C-arom.), 81.6 (C-9), 66.5 (C-12), 59.0 (C-6), 56.5 (C-3), 56.5 (C-17), 46.6 (C-2), 28.4 (C-10), 19.3 (C-4), 13.9 (C-8)

Allyl-(*S*)-(1-hydroxypropan-2-yl)carbamate (2).



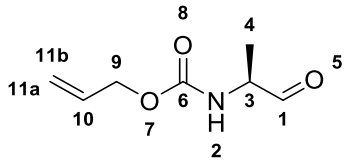
L-Alaninol (10.0 g, 133 mmol, 1.0 eq.) in ethyl acetate (26 mL) was added to sodium carbonate (42.3 g, 399 mmol, 3.0 eq.) in water (100 mL). Allyl chloroformate (17.0 mL, 160 mmol, 1.2 eq.) was added slowly while holding the temperature at 20-25 °C and the biphasic mixture was stirred vigorously for 1 h at 20-25 °C. The mixture was diluted with water (100 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over sodium sulphate. The solvent was evaporated yielding a colourless oil (20.6 g, 129 mmol, 97.3%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_7H_{14}NO_3$ m/z= 160.0968, found m/z= 160.0968.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 5.97-5.84 (m, 1H, H-10), 5.29 (ddt, ^2J=1.5 Hz, ^3J=17.2 Hz, ^4J=1.5 Hz, 1H, H-11b), 5.20 (ddt, ^2J=1.5 Hz, ^3J=10.4 Hz, ^4J=1.5 Hz, 1H, H-11a), 5.03 (s, 1H, H-2), 4.60-4.50 (m, 2H, H-9), 3.85-3.76 (m, 1H, H-3), 3.63 (dd, ^2J=11.0 Hz, ^3J=4.0 Hz, 1H, H-1a/b), 3.50 (dd, ^2J=11.0 Hz, ^3J=5.9 Hz, 1H, H-1a/b), 2.75 (s, 1H, H-5), 1.16 (d, ^3J=6.8 Hz, 3H, H-4).

^{13}C-NMR (100.61 MHz, 298K, $CDCl_3$): δ= 156.6 (C-6), 132.9 (C-10), 117.9 (C-11), 66.9 (C-1), 65.8 (C-9), 49.1 (C-3), 17.4 (C-4).

Allyl-(*S*)-(1-oxopropan-2-yl)carbamate (4)



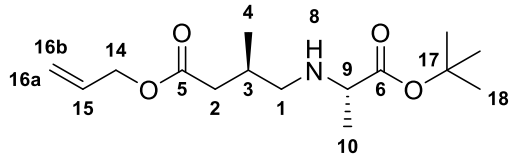
Allyl (*S*)-(1-hydroxypropan-2-yl)carbamate (**2**) (11.4 g, 71.4 mmol, 1.0 eq.), IBX (30.0 g, 107 mmol, 1.5 eq.) and sodium sulphate (5.07 g, 35.7 mmol, 0.5 eq.) were suspended in ethyl acetate (110 mL). The mixture was heated to 80 °C, DMSO (15.2 mL, 214 mmol, 3.0 eq.) was added and the mixture was stirred for 5 h at 80 °C. Then the mixture was cooled to 0-5 °C, filtered and the filter cake was washed with ethyl acetate (50 mL). The filtrate was washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL) and dried over sodium sulphate. The solvent was evaporated under reduced pressure yielding a colourless oil (9.12 g, 58.0 mmol, 81.3%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_7H_{12}NO_3$ m/z= 158.0810, found m/z= 158.0812.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 9.56 (s, 1H, H-1), 5.97-5.84 (m, 1H, H-10), 5.40 (s, 1H, H-2), 5.31 (d, ^3J=16.7 Hz, 1H, H-11b), 5.22 (ddt, ^2J=1.5 Hz, ^3J=10.4 Hz, ^4J=1.5 Hz, 1H, H-11a), 4.61-4.53 (m, 2H, H-9), 4.34-4.24 (m, 1H, H-3), 1.37 (d, ^3J=7.4 Hz, 3H, H-4).

^{13}C-NMR (100.61 MHz, 298K, $CDCl_3$): δ= 199.2 (C-1), 155.8 (C-6), 132.6 (C-10), 118.1 (C-11), 66.0 (C-9), 56.0 (C-3), 15.0 (C-4).

***tert*-Butyl ((*S*)-2-(((allyloxy)carbonyl)amino)propyl)-*L*-alaninate (S7).**



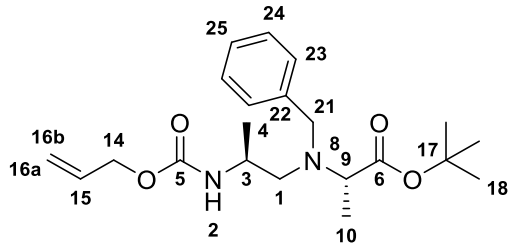
L-Alanine *tert*-butyl ester (10.3 g, 68.2 mmol, 1.2 eq.) was added to allyl (*S*)-(1-oxopropan-2-yl)carbamate (**4**) (8.93 g, 56.8 mmol, 1.0 eq.) in dichloromethane (180 mL) and the mixture was stirred for 5 min. at 20-25°C. Then sodium trisacetoxyborohydride (36.1 g, 170 mmol, 3.0 eq.) was added and the mixture was stirred for 1 h at 20-25 °C. The mixture was quenched with water (100 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (250 mL) and brine (250 mL) and dried over sodium sulphate. The solvent was evaporated under reduced pressure yielding a yellowish solid (13.8 g, 57.8 mmol, 84.8%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{14}H_{27}N_2O_4$ m/z= 287.1967, found m/z= 287.1965.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 5.91 (ddt, ^3J=17.2 Hz, 10.4 Hz, 5.6 Hz, 1H, H-15), 5.29 (ddt, ^2J=1.5 Hz, ^3J=17.2 Hz, ^4J=1.5 Hz, 1H, H-16b), 5.18 (ddt, ^2J=1.5 Hz, ^3J=10.4 Hz, ^4J=1.5 Hz, 1H, H-16a), 5.06 (s, 1H, H-2), 4.60-4.50 (m, 2H, H-14), 3.76-3.64 (m, 1H, H-3), 3.18 (q, ^3J=7.0 Hz, 1H, H-9), 2.67 (dd, ^2J=11.9 Hz, ^3J=5.2 Hz, 1H, H-1a/b), 2.47 (dd, ^2J=11.9 Hz, ^3J=6.5 Hz, 1H, H-1a/b), 1.72 (br, 1H, H-8), 1.45 (s, 9H, H-18), 1.23 (d, ^3J=7.0 Hz, 3H, H-10), 1.16 (d, ^3J=6.6 Hz, 3H, H-4).

^{13}C-NMR (100.61 MHz, 298K, $CDCl_3$): δ= 175.0 (C-6), 156.0 (C-5), 133.2 (C-15), 117.6 (C-16), 81.1 (C-17), 65.5 (C-14), 57.6 (C-9), 52.6 (C-1), 28.2 (C-3), 19.0 (C-18).

***tert*-Butyl *N*-((*S*)-2-(((allyloxy)carbonyl)amino)propyl)-*N*-benzyl-*L*-alaninate (8)**



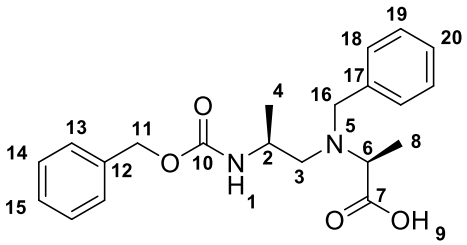
Benzylbromide (8.58 mL, 71.7 mmol, 1.5 eq.) was added to a mixture of *tert*-butyl ((*S*)-2-(((allyloxy)carbonyl)amino)propyl)-*L*-alaninate (**S7**) (13.7 g, 47.8 mmol, 1.0 eq.) and potassium carbonate (7.27 g, 52.6 mmol, 1.1 eq.) in acetonitrile (200 mL) and the mixture was stirred for 8 h at 40 °C. The mixture was filtrated, and the filtrate concentrated in vacuo. The residue was subjected to flash column chromatography (pentane → cyclohexane/ethyl acetate, 3:7, 1% NEt_3) yielding the title compound as a yellowish oil (16.0 g, 63.7 mmol, 88.8%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{21}H_{32}N_2O_4$ m/z= 377.2435, found m/z= 377.2437.

^{1}H-NMR (500.13 MHz, 298K, DMSO-d_6): δ= 7.33-7.19 (m, 5H, H-23, H-24, H-25), 6.97 (d, ^3J = 7.9 Hz, 1H, H-2), 5.89 (ddt, ^3J = 17.3 Hz, 10.5 Hz, 5.3 Hz, 1H, H-15), 5.25 (ddt, ^2J = 1.5 Hz, ^3J = 17.2 Hz, ^4J = 1.5 Hz, 1H, H-16b), 5.15 (ddt, ^2J = 1.5 Hz, ^3J = 10.5 Hz, ^4J = 1.5 Hz, 1H, H-16a), 4.49 – 4.39 (m, 2H, H-14), 3.82 (d, ^2J = 14.3 Hz, 1H, H-21a), 3.65 (d, ^2J = 14.2 Hz, 1H, H-21b), 3.60-3.49 (m, 1H, H3), 3.21 (q, ^3J = 7.1 Hz, 1H, H-9), 2.54-2.48 (m, 2H, H-1), 1.43 (s, 9H, H-18), 1.10 (d, ^3J = 7.1 Hz, 3H, H-10), 1.04 (d, ^3J = 6.6 Hz, 3H, H-4).

^{13}C-NMR (125.77 MHz, 298K, DMSO-d_6): δ= 172.2 (C-6), 155.3 (C-5), 139.7 (C-22), 133.9 (C-15), 128.3 (C-23), 128.2 (C-24), 126.8 (C-25), 116.7 (C-16), 80.2 (C-17), 64.0 (C-14), 57.1 (C-9), 55.9 (C-21), 55.5 (C-1), 45.4 (C-3), 27.9 (C-18), 18.6 (C-4), 15.6 (C-10).

***N*-Benzyl-*N*-((*S*)-2-(((Benzyloxy)carbonyl)amino)propyl)-*L*-alanine (12).**



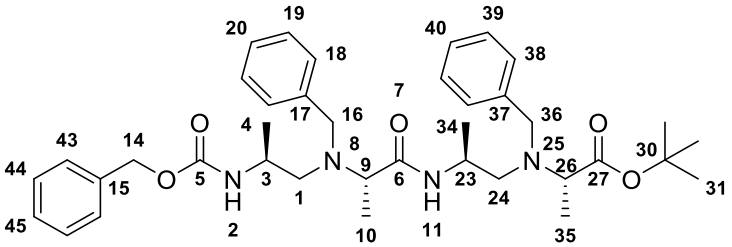
tert-Butyl-*N*-benzyl-*N*-((*S*)-2-(((benzyloxy) carbonyl)amino)propyl)-*L*-alaninate (**5**) (4.01g, 9.40 mmol, 1.0 eq.) was dissolved in hydrogen chloride solution (conc. in 1,4-dioxane, 30.0 mL). The reaction mixture was heated to 40 °C and stirred for 18 h. The solution was evaporated to dryness yielding the title compound as a hydrochloride salt (3.81g, 9.36mmol, quant.). The product was used in the next step without additional purification.

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{21}H_{27}N_2O_4$ m/z= 371.1965, found m/z= 371.1970.

^{1}H-NMR (500.13 MHz, 298K, CD_3CN): δ= 7.58-7.31 (m, 10H, H-13, H-14, H-15, H-18, H-19, H-20), 5.08 (d, ^2J=12.2 Hz, 1H, H-11a), 5.05 (d, 2J=12.2 Hz, 1H, H-11b), 4.66 (d, ^2J=12.9 Hz, 1H, H-16a), 4.17-4.06 (m, 1H, H-2), 4.07 (q, ^3J=7.2 Hz, 1H, H-6), 3.96 (d, ^2J=12.9 Hz, 1 H, H-16b), 3.22 (dd, ^2J=13.6 Hz, ^3J=1.8 Hz, 1H, H-3a), 3.10 (dd, ^2J=13.6 Hz, ^3J=10.4 Hz, 1H, H-3b), 1.55 (d, ^3J=7.2 Hz, 3H, H-8), 1.16 (d, ^3J=6.9 Hz, 3H, H-4).

^{13}C-NMR (125.75 MHz, 298K, CD_3CN): δ= 171.1 (C-7), 159.9 (C-10), 137.4 (C-12), 131.5 (C-17), 131.1 (C-18), 131.0 (C-arom.), 130.4 (C-arom.), 129.5 (C-arom.), 129.2 (C-arom.), 129.0 (C-13), 68.1 (C-11), 61.1 (C-6), 59.5 (C-3), 56.7 (C-16), 44.7 (C-2), 18.1 (C-4), 9.6 (C-8).

***tert*-Butyl (5*S*,8*S*,11*S*,14*S*)-7,13-dibenzyl-5,8,11,14-tetramethyl-3,9-dioxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (S10).**



Phenylsilane (11.1 mL, 86.5 mmol, 5.0 eq.) was added to a mixture of tetrakis(triphenylphosphine)palladium (1.00 g, 0.865 mmol, 0.05 eq.) and *tert*-butyl *N*-((*S*)-2-(((allyloxy)carbonyl)amino)propyl)-*N*-benzyl-*L*-alaninate (**8**) (6.51 g, 17.3 mmol, 1.0 eq.) in dichloromethane (100 mL) and the mixture was stirred for 4 h at 20-25 °C. In a separate flask, 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-ox-id hexafluorophosphate (13.0 g, 34.2 mmol, 2.0 eq.) was added to *N*-benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-alanine hydrochloride (**12**) (6.96 g, 17.1 mmol, 1.0 eq.), DIPEA (11.3 mL, 68.4 mmol, 4.0 eq.) in dichloromethane (100 mL) and the mixture was stirred for 5 min. at 20-25 °C. The activated carboxylic acid was then slowly added to the deprotected amino compound and the mixture was stirred for 4 h at 20-25 °C. The reaction was quenched with 0.1 M HCl (50 mL) and the mixture was stirred for 30 min. at 20-25 °C. The layers were separated, and the organic layer was concentrated in vacuo. The residue was subjected to column chromatography (SiO_2, cyclohexane / ethyl acetate, 7:3, dry load) to give *tert*-butyl (5*S*,8*S*,11*S*,14*S*)-7,13-dibenzyl-5,8,11,14-tetramethyl-3,9-dioxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (7.13 g, 0.560 mmol, 64.7%).

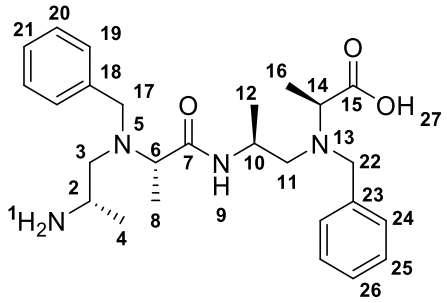
HR-ESI-MS: calcd. for $[M+H]^+$ $C_{38}H_{53}N_4O_5$ m/z= 645.4010, found m/z= 645.4008.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 7.47 (s, 1H, H-11), 7.39 – 7.14 (m, 15H, H-18, H-19, H-20, H-38, H-39, H-40, H-43, H-44, H-45), 5.11 (d, ^2J = 12.1 Hz, 1H, H-14a), 4.96 (d, ^2J = 12.4 Hz, 1H, H-14b), 4.94 (s, 1H, H-2), 4.06 – 3.94 (m, 1H, H-23), 3.99 (d, ^2J = 14.3 Hz, 1H, H-36a), 3.88 – 3.80 (m, 1H, H-3), 3.80 (d, ^2J = 13.1 Hz, 1H, H-36b), 3.77 (d, ^2J = 13.0 Hz, 1H, H-16a), 3.48 (d, ^2J = 12.8 Hz, 1H, H-16b), 3.48 – 3.42 (m, 1H, H-9), 3.35 (q, ^3J = 7.1 Hz, 1H, H-26), 2.73 (dd, ^2J = 13.2 Hz, ^3J = 6.5 Hz, 1H, H-24a), 2.65 (dd, ^2J = 13.3, ^3J = 7.4 Hz, 1H, H24-b), 2.59 (d, ^2J = 13.2 Hz, ^3J = 7.9 Hz, 1H, H-1a), 2.43 (dd, ^2J = 13.6 Hz, ^3J = 3.5 Hz, 1H,

H-1b), 1.44 (s, 9H, H-31), 1.24 (d, ^3J = 6.9 Hz, 3H, H-10), 1.19 (d, ^3J = 7.6 Hz, 3H, H-35), 1.18 (d, ^3J = 6.8 Hz, 3H, H-42), 1.07 (d, ^3J = 6.6 Hz, 3H, H-4).

^{13}C-NMR (125.77 MHz, 298K, $CDCl_3$): δ= 173.2 (C-27), 172.7 (C-6), 156.5 (C-5), 139.3 (C-37), 138.2 (C-17), 136.7 (C-15), 129.3 (C-arom.), 128.8 (C-arom.), 128.6 (C-arom.), 128.6 (C-arom.), 128.4 (C-arom.), 128.2 (C-arom.), 127.6 (C-arom.), 127.2 (C-arom.), 81.3 (C-30), 66.7 (C-14), 58.8 (C-9), 58.0 (C-26), 56.5 (C-1), 56.4 (C-36), 55.8 (C-24), 55.2 (C-16), 45.2 (C-3), 44.4 (C-23), 28.4 (C-31), 19.4 (C-4), 19.0 (C-42), 14.9 (C-35), 8.9 (C-10).

_N_-((_S_)-2-((_S_)-2-(((_S_)-2-aminopropyl)(benzyl)amino)propanamido)propyl)-_N_-benzyl-_L_-alanine (14).



tert-Butyl (5*S*,8*S*,11*S*,14*S*)-7,13-dibenzyl-5,8,11,14-tetramethyl-3,9-dioxo-1phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (**S10**) (1.73 g, 2.68 mmol, 1.0 eq.) was dissolved in hydrobromic acid solution (16% wt. in acetic acid, 15.0 mL) and stirred at 40 °C for 30 min. The solvent was removed under reduced pressure yielding a brownish oil. This oil was further suspended in acetonitrile (15 mL) and hydrochloric acid (37%, 5.0 mL). This mixture was again evaporated to dryness. The procedure was repeated three times to remove residual acetic acid from the product. Finally, the product was dissolved in methanol (15.0 mL) and evaporated to dryness, yielding a light brown foam. This foam was extensively dried under high vacuum at 40 °C for 2 d. The product (1.89 g) is obtained as a mixture of HCl and HBr salt with minimal acetate content and was further used without additional purification.

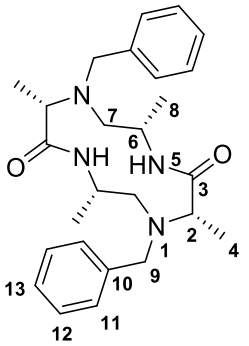
HR-ESI-MS: calcd. for $[M+H]^+$ $C_{26}H_{39}N_4O_3$ m/z= 455.3017, found m/z= 455.3022.

^{1}H-NMR(500.13 MHz, 298K, DMSO-d_6): δ = 9.96 (bs, 1H, H-27), 8.64 (bs, 2H, H-1), 7.51-7.40 (m, 2H, H-arom.), 7.35-7.22 (m, 5H, H-arom.), 7.21-7.11 (m, 3H, H-arom.), 3.67 (d, ^2J = 14.5 Hz, 1H, H-22a), 3.62 (d, ^2J = 14.5Hz, 1H, H-22b), 3.61 (m, 1H, H-10), 3.44 (q, ^3J = 6.9 Hz, 1H, H-6), 3.47 (d, ^2J = 14.1 Hz, 1H, H-17a), 3.42 (d, ^2J = 14.2 Hz, 1H, H-17b), 3.32-3.24 (m, 1H, H-2), 2.99 (q, ^3J = 7.3 Hz, 1H, H-14), 2.77 (dd, ^2J = 13.8 Hz, ^3J = 11.5 Hz, 1H, H-11a), 2.54 (dd, ^2J = 13.6 Hz, ^3J = 8.6 Hz, 1H, H-3a), 2.39-2.31 (m, 2H, H-11b, H-3b), 1.10 (d, ^3J = 6.9 Hz, 3H, H-8), 1.08 (d, ^3J = 7.0 Hz, 3H, H-16), 1.00 (d, ^3J = 6.5 Hz, 3H, H-4), 0.98 (d, ^3J = 6.2 Hz, 3H, H-12).

^{13}C-NMR(125.77 MHz, 298K, DMSO-d_6): δ = 177.4 (C-15), 171.5 (C-7), 140.7 (C-23), 138.5 (C-18), 129.0 (C-arom.), 128.2 (C-arom.), 128.1 (C-arom.), 128.0 (C-arom.), 126.9 (C-arom.), 126.4 (C-arom.), 59.1 (C-14), 57.4 (C-6), 55.9 (C-22), 55.0 (C-11), 53.6 (C-17), 53.5 (C-3), 44.6 (C-10), 43.3 (C-2), 18.3 (C-12), 17.4 (C-4), 10.8 (C-8), 10.2 (C-16).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{26}H_{39}N_4O_3$ m/z= 455.3017, found m/z= 455.3022.

(3*S*,6*S*,9*S*,12*S*)-4,10-dibenzyl-3,6,9,12-tetramethyl-1,4,7,10-tetraazacyclododecane-2,8-dione (17).



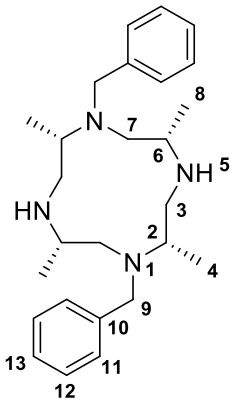
N-((*S*)-2-((*S*)-2-(((*S*)-2-aminopropyl)(benzyl)amino)propanamido)propyl)-*N*-benzyl-*L*-alanine (**14**) (1.89 g, 2.68 mmol, 1.0 eq.) and *N*-ethyl diisopropylamine (2.2 mL, 13.4 mmol, 5.0 eq.) were dissolved in acetonitrile (1.8 L). HATU (1.26 g, 3.22 mmol, 1.2 eq.) was added and the solution was stirred at 20-25°C for 20 min. The solvent was removed under vacuum. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate / cyclohexane (7:3)) yielding a white solid (950 mg, 2.18 mmol, 81.2% yield calculated over 2 steps).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{26}H_{37}N_4O_2$ m/z= 437.2911, found m/z= 437.2917.

^{1}H-NMR(600.13 MHz, 298K, DMSO-d_6): δ = 7.73 (d, ^3J = 4.8 Hz, 2H, H-5), 7.45-7.42 (m, 4H, H-11), 7.33-7.25 (m, 6H, H-12, H-13), 3.90 (d, ^2J = 13.3 Hz, 2H, H-9a), 3.57 (d, ^2J = 13.3 Hz, 2H, H-9b), 3.34 (dddq, ^3J = 10.8 Hz, ^3J = 4.8 Hz, ^3J = 2.8 Hz, ^3J = 6.6 Hz, 2H, H-6), 3.20 (q, ^3J = 7.0 Hz, 2H, H-2), 2.77 (dd, ^2J = 13.4 Hz, ^3J = 10.8 Hz, 2H, H-7a), 2.29 (dd, ^2J = 13.4 Hz, ^3J = 2.8 Hz, 2H, H-7b), 1.15 (d, ^3J = 6.6 Hz, 6H, H-8), 1.05 (d, ^3J = 7.0 Hz, 6H, H-4).

^{13}C-NMR(150.95 MHz, 298K, DMSO-d_6): δ = 172.1 (C-3), 139.2 (C-10), 129.1 (C-11), 128.2 (C-12), 127.1 (C-13), 59.7 (C-2), 56.9 (C-9), 55.1 (C-7), 44.1 (C-6), 17.7 (C-8), 8.5 (C-4).

(2*S*,5*S*,8*S*,11*S*)-1,7-dibenzyl-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane (20).



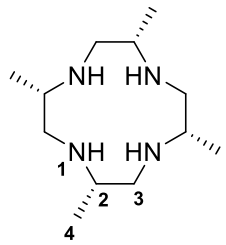
(3*S*,6*S*,9*S*,12*S*)-4,10-dibenzyl-3,6,9,12-tetramethyl-1,4,7,10-tetraazacyclododecane-2,8-dione (**17**) (1.90 g, 4.35 mmol, 1.0 eq.) was dissolved in dichloromethane (50 mL) and cooled to 0-5 °C. Trimethylsilyl chloride (2.60 g, 23.9 mmol, 5.5 eq.) was slowly added. After completion, the reaction mixture was stirred at 0-5 °C for 30 min followed by the addition of lithium aluminium hydride (6.1 mL, 2 M in THF, 12.2 mmol, 2.8 eq.). The reaction mixture was allowed to warm to 20-25 °C and was further stirred for 3 h. The reaction mixture was cooled to 0-5 °C and saturated aqueous sodium hydrogen carbonate (5 mL) was slowly added. To the resulting suspension sodium sulphate (5 g) was added. The suspension was filtered and evaporated to dryness yielding a white solid (1.65 g, 4.04 mmol, 92.8%).

^{1}H-NMR (600.13 MHz, 298K, $CDCl_3$): δ= 7.40-7.34 (m, 4H, H-11, H-12), 7.29-7.26 (m, 1H, H-13), 3.81 (d, ^{2}J=12.8 Hz, 1H, H-9a), 3.13-3.02 (bs, 1H, H-6), 2.98 (d, ^2J=12.8 Hz, 1H, H-9b), 2.94 (bs, 1H, H-5), 2.88-2.76 (m, 2H, H-2, H-7a), 2.45 (d, ^2J=11.8 Hz, 1H, H-3a), 2.40 (dd, ^2J=13.4 Hz, ^3J=13.1 Hz, 1H, H-7b), 2.25 (dd, ^2J=11.8 Hz, ^3J=11.8 Hz, 1H, H-3b), 0.91 (d, ^3J=6.5 Hz, 3H, H-8), 0.87 (d, ^3J=5.5 Hz, 3H, H-4).

^{13}C-NMR (150.9 MHz, 298K, $CDCl_3$): δ= 139.97 (C-10), 129.41 (C-12), 128.50 (C-11), 127.30 (C-13), 56.62 (C-3), 51.72 (C-9), 50.04 (C-6), 47.83 (C-7), 46.47 (C-2), 18.71 (C-4), 10.20 (C-8).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{26}H_{41}N_4$ m/z=409.3326, found m/z=409.3330.

(2S,5S,8S,11S)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane (M4-cyclen).



(2*S*,5*S*,8*S*,11*S*)-1,7-dibenzyl-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane (**20**) (1.5 g, 3.67 mmol, 1.0 eq), palladium hydroxide on carbon (750 mg, 20 wt% loading) and ammonium formate (5.0 g, 79.3 mmol, 10.0 eq) were suspended in ethanol (50 mL) and heated to reflux. The suspension was refluxed for 16 h, cooled to 20-25 °C, filtered over celite and evaporated to dryness. The crude product was washed with cold acetone (1 mL). The title compound was obtained as a white solid (0.65 g, 2.84 mmol, 77.6%).

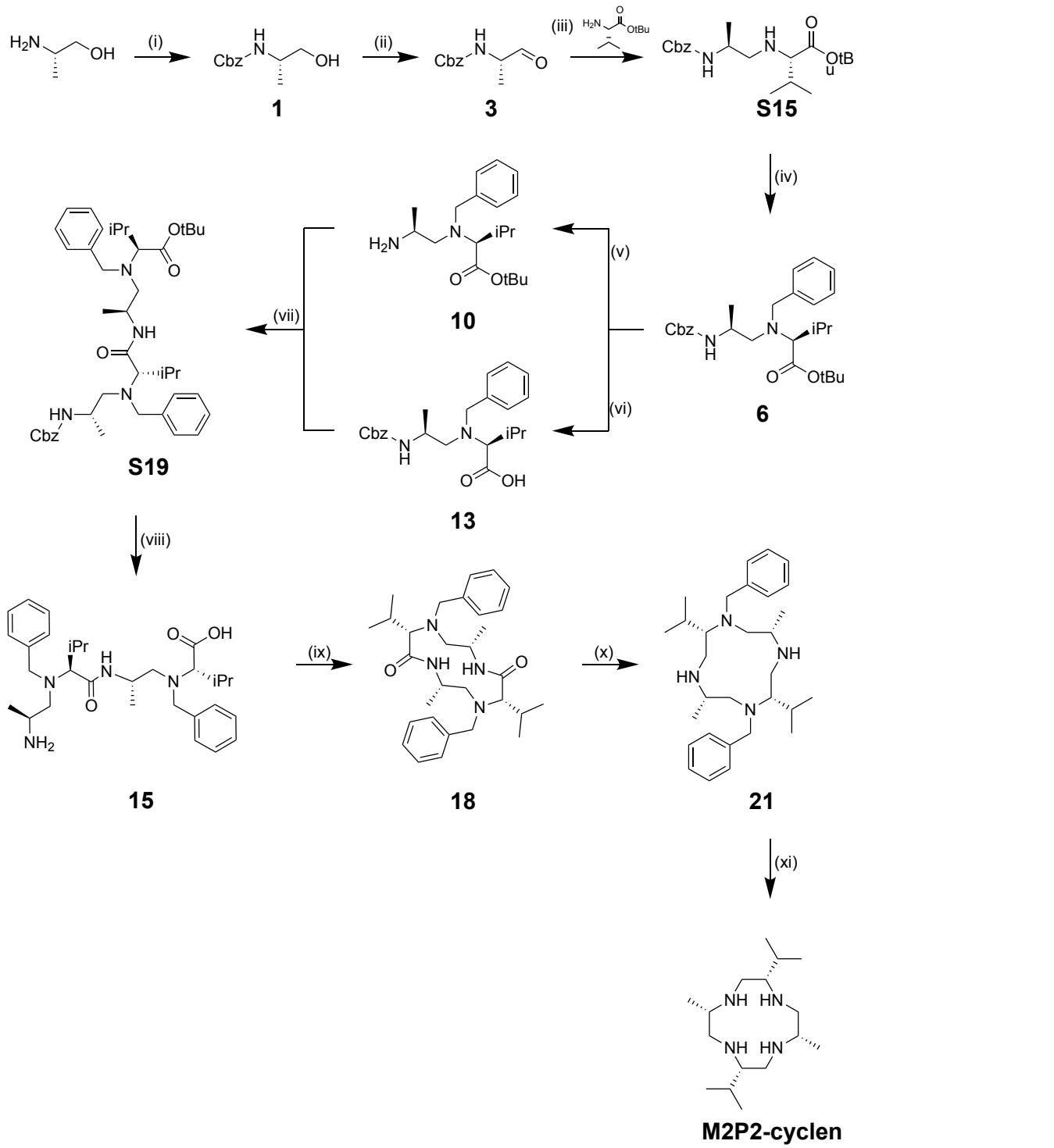
ESI-MS: calcd. for $[M+H]^+$ $C_{12}H_{29}N_4$ m/z=229.23, found m/z=229.15.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 2.70-2.60 (m, 8H, H-2, H-3eq), 2.38 (dd, ^2J=13.4 Hz, ^3J=10.6 Hz, 4H, H-3ax), 2.01 (bs, 4H, H-1), 0.95 (d, ^3J=6.1 Hz, 12H, H-4).

^{13}C-NMR (125.77 MHz, 298K, $CDCl_3$): δ= 52.32 (C-2), 47.67 (C-3), 18.42 (C-4).

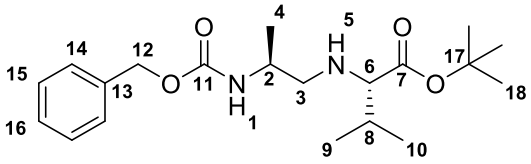
$[\alpha_D^{20}]$ + 182.7° (c 1.00, $CHCl_3$).

SYNTHESIS OF M2P2-CYCLEN



Scheme S2: Synthetic route towards M2P2-cyclen. Reaction conditions. i) Cbz-Cl, Na_2CO_3, H2O, EtOAc, 20-25 °C, 1 h; ii) IBX, DMSO, EtOAc, RF, 3.5 h; iii) $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 16 h; iv) BnBr, K_2CO_3, MeCN, 60 °C, 2 d; v) 5% Pd/$BaSO_4$, MeOH, 20-25 °C, 3 h; vi) HCl in dioxane, 40 °C, 16 h; vii) HATU, DIPEA, MeCN, 20-25°C, 4 h; viii) HBr in AcOH 16 wt. %, 40 °C, 30 min; ix) HATU, DIPEA, MeCN, 20-25 °C, 20 min; x) TMS-Cl, $LiAlH_4$, THF/CH_2Cl_2, 0-5 °C → 20-25 °C; xi) ammonium formate, Pd/C, EtOH, RF, 16 h.

***tert*-Butyl ((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-valinate (S15).**



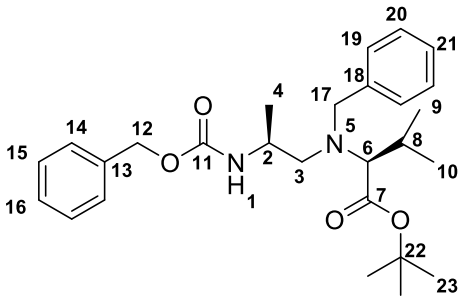
Benzyl (*S*)-(1-oxopropan-2-yl)carbamate (**3**) (12.6 g, 60.8 mmol, 1.0 eq.) was dissolved in dichloromethane (120 mL). To this solution, *L*-valine *tert*-butyl ester (10.7 g, 62.0 mmol, 1.02 eq.) was added. The solution was stirred at 20-25 °C for 5 min. followed by the addition of sodium triacetoxyborohydride (52.3 g, 0.25 mol, 4.1 eq.). The reaction mixture was stirred at 20-25 °C for 16 h. The excess of sodium triacetoxyborohydride was quenched with aqueous saturated sodium hydrogen carbonate (150 mL) and the pH adjusted to >9 by addition of triethylamine (20 mL). The two layers were separated, and the organic layer was washed with aqueous saturated sodium hydrogen carbonate (2 x 100 mL), water (50 mL) and dried with sodium sulphate. The organic layer was evaporated to dryness and the crude oil was purified by flash column chromatography (SiO_2, cyclohexane/ethyl acetate (7:3) 1% NEt_3) yielding a yellowish oil (19.4 g, 53.2 mmol, 87.5%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{20}H_{33}N_2O_4$ m/z=365.2435, found m/z=365.2439.

^{1}H-NMR (400.13 MHz, 298K, CD_3CN): δ= 7.41-7.25 (m, 5H, H-14, H-15, H-16), 5.56 (bs, 1H, H-1), 5.06 (d, ^{2}J=13.4 Hz, 1H, H-12a), 5.02 (d, ^{2}J=13.4 Hz, 1H, H-12b), 3.61 (qdd, ^{3}J=6.6 Hz, ^{3}J=6.4 Hz, ^{3}J=5.8 Hz, 1H, H-2), 2.76 (d, ^{3}J=6.3 Hz, 1H, H-6), 2.62 (dd, ^{2}J=11.9 Hz, ^{3}J=5.8 Hz, 1H, H-3a), 2.37 (dd, ^{2}J=11.9 Hz, 6.4 Hz, 1H, H-3b), 1.81 (dqq, ^{3}J=6.3 Hz, ^{3}J=6.8 Hz, ^{3}J=6.8 Hz, 1H, H-8), 1.44 (s, 9H, H-18), 1.17 (d, ^{3}J=6.6 Hz, 3H, H-9/10), 0.91 (d, ^{3}J=6.8 Hz, 3H, H-9/10), 0.90 (d, ^{3}J=6.8 Hz, 3H, H-9/10) .

^{13}C-NMR (100.61 MHz, 298K, CD_3CN): δ= 171.15 (C-7), 156.88 (C-11), 138.54 (C-13), 129.41 (C-15), 128.77 (C-16), 128.66 (C-14), 81.36 (C-17), 69.20 (C-6), 66.59 (C-12), 54.20 (C-3), 48.32 (C-2), 32.42 (C-8), 28.35 (C-18), 19.66 (C-9/10), 19.02 (C-4), 18.94 (C-9/10).

***tert*-Butyl *N*-benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-valinate (6).**



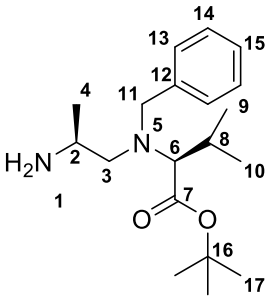
tert-Butyl ((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-valinate (**S15**) (19.4 g, 53.2 mmol, 1.0 eq.) was dissolved in acetonitrile (200 mL) and potassium carbonate (8.09 g, 58.5 mmol, 1.1 eq.) was added. To this suspension benzyl bromide (9.5 mL, 79.8 mmol, 1.5 eq.) was added over a period of 5 minutes. The reaction mixture was heated to 60 °C and stirred for 2 days under an argon atmosphere. Excess of benzyl bromide was quenched with NEt_3 (30 mL). The suspension was stirred at 50 °C for 30 minutes and an additional 30 minutes at 20-25 °C. The reaction mixture was filtered, washed with acetonitrile (50 mL) and evaporated to dryness. The crude oil was purified by flash column chromatography (SiO_2, cyclohexane/ethyl acetate (8:2) 1% NEt_3) yielding a colourless oil (21.0 g, 46.2 mmol, 86.9%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{27}H_{39}N_2O_4$ m/z=455.2904, found m/z= 455.2908.

^{1}H-NMR (400.13 MHz, 298K, CD_3CN): δ= 7.36-7.15 (m, 10H, H-19, H-20, H-21, H-14, H-15, H-16), 5.47 (bs, 1H, H-1), 5.02 (d, ^{2}J=12.5 Hz, 1H, H-12a), 4.96 (d, ^{2}J=12.5 Hz, 1H, H-12b), 3.96 (d, ^{2}J=14.0 Hz, 1H, H-17a), 3.72 (ddq, ^{3}J=8.8 Hz, ^{3}J=5.5 Hz, ^{3}J=6.2 Hz), 3.41 (d, ^{2}J=14.0 Hz, 1H, H-17b), 2.63 (d, ^{3}J=10.8 Hz, 1H, H-6), 2.57 (dd, ^{2}J=13.0 Hz, ^{3}J=8.8 Hz, 1H, H-3a), 2.49 (dd, ^{2}J=13.0 Hz, ^{3}J=5.5 Hz, 1H, H-3b), 1.97 (ddq, ^{3}J=10.8 Hz, ^{3}J=6.5 Hz, ^{3}J=6.5 Hz, 1H, H-8), 1.47 (s, 9H, H-23), 1.08 (d, ^{3}J=6.6 Hz, 3H, H-4), 0.95 (d, ^{3}J=6.5 Hz, 3H, H-9/10), 0.81 (d, ^{3}J=6.5 Hz, 3H, H-9/10).

^{13}C-NMR (100.61 MHz, 298K, CD_3CN): δ= 172.07 (C-7), 156.65 (C-11), 140.84 (C-18), 138.47 (C-13), 129.92 (C-20), 129.36 (C-21), 129.05 (C-19), 128.74 (C-15), 128.64 (C-16), 127.82 (C-14), 81.68 (C-22), 71.04 (C-6), 66.56 (C-12), 56.96 (C-3), 56.71 (C-17), 46.77 (C-2), 28.55 (C-23), 28.27 (C-8), 20.11 (C-9/10), 20.10 (C-9/10), 19.41 (C-4).

***tert*-Butyl *N*-((*S*)-2-aminopropyl)-*N*-benzyl-*L*-valinate (10).**



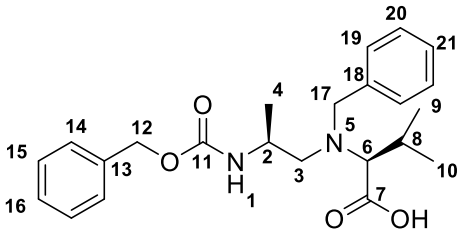
tert-Butyl *N*-benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-valinate (**6**) (10.7 g, 23.5 mmol, 1.0 eq.) was dissolved in methanol (100 mL). Palladium on barium sulphate (1.8 g, 5% $Pd/BaSO_4$) was added and the reaction flask was flushed with nitrogen. Then hydrogen was bubbled through the solution for 5 minutes and the reaction mixture was left stirring under a hydrogen atmosphere for 3 h. The suspension was filtered over celite and washed with methanol (3 x 50 mL). The filtrate was evaporated to dryness yielding a slightly yellowish oil (6.82 g, 21.3 mmol, 90.6%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{19}H_{33}N_2O_2$ m/z=321.2537, found m/z=321.2539.

^{1}H-NMR (400.13 MHz, 298K, DMSO-d_6): δ= 7.40-7.16 (m, 5H, H-13, H-14, H-15), 3.93 (d, ^{2}J=14.1 Hz, 1H, H-11a), 3.35 (d, ^{2}J=14.1 Hz, 1H, H-11b), 3.27 (bs, 3H, H-1), 2.96 (m, 1H, H-2), 2.60 (d, ^{3}J=10.8 Hz, 1H, H-8), 2.42 (dd, ^{2}J=13.1 Hz, ^{3}J=8.9 Hz, 1H, H-3a), 2.35 (dd, ^{2}J=13.1 Hz, 5.3 Hz, 1H, H-3b), 1.93 (dqq, ^{3}J=10.8 Hz, ^{3}J=6.6 Hz, ^{3}J=6.5 Hz, 1H, H-8), 1.47 (s, 9H, H-17), 0.97 (d, ^{3}J=6.3 Hz, 3H, H-4), 0.90 (d, ^{3}J=6.6 Hz, 3H, H-9/10), 0.76 (d, ^{3}J=6.6 Hz, 3H, H-9/10).

^{13}C-NMR (100.61 MHz, 298K, DMSO-d_6): δ= 170.32 (C-7), 139.56 (C-12), 128.64 (C-14), 128.12 (C-13), 126.87 (C-15), 80.33 (C-16), 69.76 (C-6), 58.57 (C-3), 55.44 (C-11), 44.80 (C-2), 28.01 (C-17), 26.81 (C-8), 20.87 (C-4), 19.58 (C-9/10), 19.42 (C-9/10).

***N*-Benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-valine (13).**



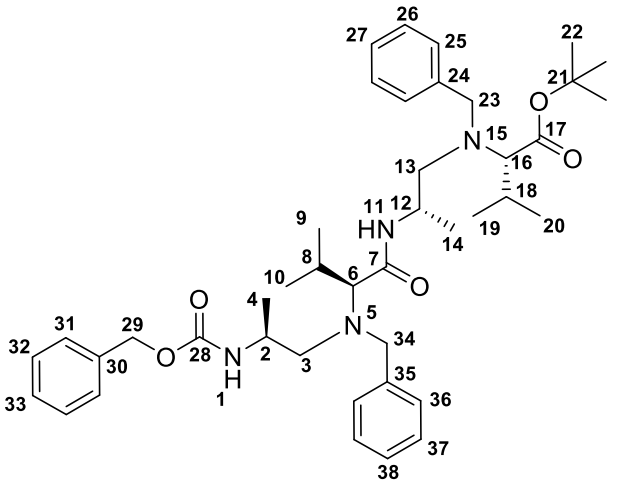
tert-Butyl *N*-benzyl-*N*-((*S*)-2-(((benzyloxy) carbonyl)amino)propyl)-*L*-valinate (**6**) (5.77 g, 12.7 mmol, 1.0 eq.) was dissolved in concentrated HCl in dioxane (50 mL) and heated to 40 °C for 16 h. The reaction mixture was then evaporated to dryness yielding the title compound as a hydrochloride salt (5.41 g, 12.4 mmol, 98%, mixture of diastereomers <10%). The product was used in the next step without further purification.

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{23}H_{31}N_2O_4$ m/z=399.2278, found m/z= 399.2283.

^{1}H-NMR (400.13 MHz, 298K, CD_3CN): δ= 7.46-6.90 (m, 10H, H-14, H-15, H-16, H-18, H-19, H-20), 5.57 (d, ^{3}J=8.1 Hz, 1H, H-1), 5.05 (d, ^{2}J=12.6 Hz, 1H, H-12a), 4.92 (d, ^{2}J=12.6 Hz, 1H, H-12b), 4.08 (d, ^{2}J=14.6 Hz, 1H, H-17a), 3.91 (m, 1H, H-2), 3.21 (^{2}J=14.6 Hz, 1H, H-17b), 2.79 (d, ^{3}J=10.6 Hz, 1H, H-6), 2.64 (dd, ^{2}J=12.1 Hz, ^{3}J=3.6 Hz, 1H, H-3a), 2.12-1.97 (m, 2H, H-3b, H-8), 1.03 (d, ^{3}J=6.5 Hz, 3H, H-4), 0.96 (d, ^{3}J=6.6 Hz, 3H, H-9/10), 0.90 (d, ^{3}J=6.4 Hz, 3H, H-9/10).

^{13}C-NMR (100.61 MHz, 298K, CD_3CN): δ= 177.55 (C-7), 156.37 (C-11), 141.25 (C-18), 136.52 (C-13), 128.43 (C-arom.), 128.10 (C-arom.), 127.61 (3C, C-arom.), 125.98 (C-arom.), 71.86 (C-6), 65.94 (C-12), 55.99 (C-3), 53.55 (C-17), 44.19 (C-2), 26.83 (C-8), 19.81 (C-9/10), 18.93 (C-9/10), 16.88 (C-4).

***tert*-Butyl (5*S*,8*S*,11*S*,14*S*)-7,13-dibenzyl-8,14-diisopropyl-5,11-dimethyl-3,9-dioxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (S19).**



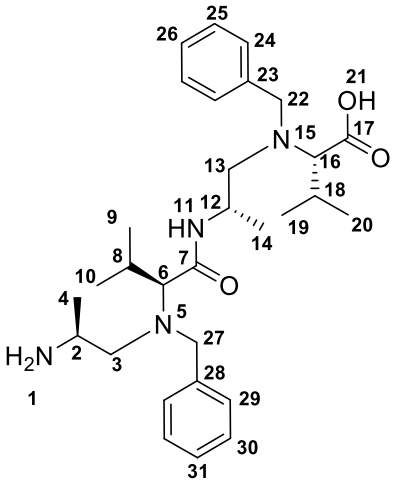
N-Benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-valine (**13**) hydrochloride (5.00 g, 11.5 mmol, 1.0 eq.), *tert*-butyl *N*-((*S*)-2-aminopropyl)-*N*-benzyl-*L*-valinate (**10**) (3.64 g, 11.4 mmol, 1.01 eq.) and DIPEA (6.00 mL, 36.3 mmol, 3.2 eq.) were dissolved in acetonitrile (70 mL). To this solution, HATU (4.93 g, 13.0 mmol, 1.14 eq.) was added. After 40 minutes, additional HATU (1.06 g, 2.79 mmol, 0.2 eq.) was added and the solution was stirred for another 2h. The solvent was removed under reduced pressure and the crude oil was purified by flash column chromatography (SiO_2, pentane/methyl *tert*-butyl ether (7:3) 1% NEt_3) yielding a colourless oil (6.05 g, 8.63 mmol, 75.7%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{42}H_{61}N_4O_5$ m/z=701.4636, found m/z=701.4640.

^{1}H-NMR (600.13 MHz, 343K, DMSO-d_6): δ= 7.44-7.21 (m, 15H, H-25, H-26, H-27, H-31, H-32, H-33, H-36, H-37, H-38), 5.00 (d, ^{2}J=12.9 Hz, 1H, H-29a), 4.98 (d, ^{2}J=12.9 Hz, 1H, H-29b), 4.09 (m, 1H, H-12), 4.02 (d, ^{2}J=14.0 Hz, 1H, H-23a), 4.00 (d, ^{2}J=13.7 Hz, 1H, H-34a), 3.60 (bs, 1H, H-2), 3.48 (bs, 1H, H-34b), 3.41 (d, ^{2}J=14.0 Hz, 1H, H-23b), 2.79 (bs, 1H, H-6), 2.72 (d, ^{3}J=10.4 Hz, 1H, H-16), 2.65-2.59 (m, 1H, H-3a), 2.57-2.51 (m, 1H, H-3b), 2.54-2.48 (m, 2H, H-13), 2.06 (m, 1H, H-8), 1.97 (dqq, ^{3}J=10.4 Hz, ^{3}J=6.5 Hz, ^{3}J=6.5 Hz, 1H, H-18), 1.46 (s, 9H, H-22), 1.08 (d, ^{3}J=6.7 Hz, 3H, H-14), 0.99 (d, ^{3}J=6.7 Hz, 3H, H-10/9), 0.96 (d, ^{3}J=6.7 Hz, 3H, H-4), 0.94 (d, ^{3}J=6.5 Hz, 3H, H-19/20), 0.82 (d, ^{3}J=6.5 Hz, 3H, H-9/10), 0.815 (d, ^{3}J=6.5 Hz, 3H, H19/20).

^{13}C-NMR (extracted from HMBC/HMQC 600.13 MHz, 343K, DMSO-d_6): δ= 169.45 (C-17), 155.00 (C-28), 138.59 (C-24), 136.37 (C-30), 127.48 (C-25), 126.8 (C-31), 79.86 (C-21), 69.82 (C-6), 69.05 (C-16), 64.70 (C-29), 56.18 (C-3), 55.43 (C-13), 55.02 (C-34), 54.65 (C-23), 44.83 (C-2), 42.40 (C-12), 27.49 (C-22), 26.22 (C-18), 26.08 (C-8), 19.26 (C-9/10), 18.92 (C-19/20), 18.89 (C-9/10), 18.86 (C-19/20), 18.42 (C-14), 17.97 (C-4).

***N*-((*S*)-2-((*S*)-2-(((*S*)-2-aminopropyl)(benzyl)amino)-3-methylbutanamido)propyl)-*N*-benzyl-*L*-valine (15).**



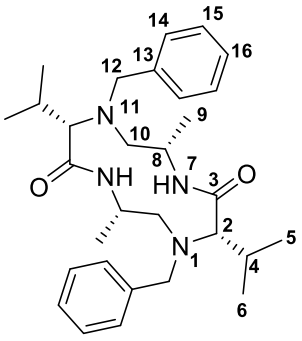
tert-Butyl (5*S*,8*S*,11*S*,14*S*)-7,13-dibenzyl-8,14-diisopropyl-5,11-dimethyl-3,9-dioxo-1-phenyl-2-oxa-4,7,10,13-tetraazapenta-decan-15-oate (**S19**) (8.55 g, 12.2 mmol, 1.0 eq.) was dissolved in acetic acid (60 mL) and hydrobromic acid solution (33 wt. % in acetic acid, 60 mL) was added. The solution was stirred at 40 °C for 30 minutes and evaporated to dryness. This oil was further suspended in acetonitrile (20 mL) and hydrochloric acid (1 mL, 37% aq.). This mixture was again evaporated to dryness. This procedure was repeated three times to remove residual acetic acid from the product. Finally, methanol (20 mL) was added and the solvent was removed under reduced pressure yielding a yellowish foam. This foam was extensively dried under high vacuum at 40 °C for 2 days. The product (9.04 g) is obtained as a mixture of HCl and HBr salt with minimal acetate content and was further used without additional purification.

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{30}H_{47}N_4O_3$ m/z=511.3643, found m/z=511.3650.

^{1}H-NMR (500.13 MHz, 298K, DMSO-d_6): δ= 7.81-7.71 (m, 3H, H-1,H-11), 7.39 -7.21 (m, 10H, H-24, H-25, H-26, H-29, H-30, H-31), 4.10-4.03 (m, 1H, H-12), 3.98 (d, ^{2}J=14.0 Hz, 1H, H-22a), 3.91 (d, ^{2}J=14.6 Hz, 1H, H-27a), 3.40 (d, ^{2}J=14.6 Hz, 1H, H-27b), 3.35 (d, ^{2}J=14.0 Hz, 1H, H-22b), 3.28-3.17 (m, 1H, H-2), 2.70 (d, ^{3}J=10.8 Hz, 1H, H-16), 2.67-2.57 (m, 2H, H-3), 2.59 (d, ^{3}J=10.8 Hz, 1H, H-6), 2.49-2.39 (m, 2H, H-13), 2.02-1.96 (m, 2H, H-18, H-8), 1.11 (d, ^{3}J=6.6 Hz, 3H, H-14), 1.06 (d, ^{3}J=6.5 Hz, 3H, H-4), 0.97 (d, ^{3}J=6.5 Hz, 3H, H-9/10), 0.95 (d, ^{3}J=6.5 Hz, 3H, H-19/20), 0.82 (d, ^{3}J=6.5 Hz, 3H, H-19/20), 0.78 (d, ^{3}J=6.5 Hz, 3H, H-9/10).

^{13}C-NMR (125.75 MHz, 298K, DMSO-d_6): δ= 172.19 (C-17), 169.39 (C-7), 139.86 (C-28) 139.44 (C-23), 128.78 (C-24), 128.39 (C-29), 128.26 (C-25), 128.17 (C-30), 126.94 (C-31), 126.88 (C-26), 69.82 (C-6), 68.74 (C-16), 55.58 (C-27), 55.47 (C-13), 55.06 (C-22), 53.68 (C-3), 44.92 (C-2), 42.66 (C-12), 26.70 (C-8), 26.62 (C-18), 19.83 (2C, C-19/20, C-9/10), 19.75 (C-9/10), 19.55 (C-19/20), 19.21 (C-14), 16.66 (C-4).

(3*S*,6*S*,9*S*,12*S*)-4,10-dibenzyl-3,9-diisopropyl-6,12-dimethyl-1,4,7,10-tetraazacyclododecane-2,8-dione (18)



A total of 9.03 g of *N*-((*S*)-2-((*S*)-2-(((*S*)-2-aminopropyl)(benzyl)amino)-3-methylbutanamido)propyl)-*N*-benzyl-*L*-valine (**15**) salt was cyclized in several portions of max. 2.0 g. *N*-((*S*)-2-((*S*)-2-(((*S*)-2-aminopropyl)(benzyl)amino)-3-methylbutanamido)propyl)-*N*-benzyl-*L*-valine (**15**) salt (2.00 g, ~4 mmol, 1.0 eq.) and *N*-ethyl diisopropylamine (3.4 mL, 20.4 mmol, 5 eq.) were dissolved in

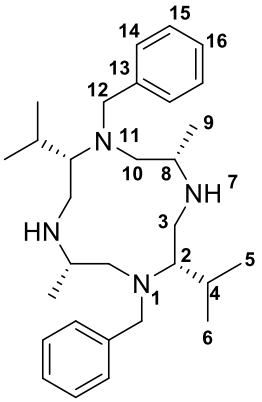
acetonitrile (2.0 L). HATU (1.55 g, ~ 4 mmol, 1.0 eq.) was added and the solution was stirred at 20-25 °C for 20 min. The solvent was removed under vacuum. The crude product from all batches was combined and purified by flash column chromatography (SiO_2, ethyl acetate / cyclohexane (9:1) 1% NEt_3) yielding a slightly yellowish solid (3.54 g, 7.2 mmol, 58.9 % yield calculate for 2 steps starting from **S19**).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{30}H_{45}N_4O_2$ m/z=493.3537, found m/z=493.3539.

^{1}H-NMR (600.13 MHz, 298K, $CDCl_3$): δ= 7.37-7.23 (m, 10H, H-14, H-15, H-16), 3.98 (d, ^{2}J=14.2 Hz, 2H, H-12a), 3.90 (d, ^{2}J=14.2 Hz, 2H, H-12b), 3.74-3.64 (m, 2H, H-8), 3.20 (dd, ^{2}J=13.7 Hz, ^{3}J=11.3 Hz, 2H, H-10a), 2.96 (d, ^{3}J=8.1 Hz, 2H, H-4), 2.72 (dd, ^{2}J=13.7 Hz, ^{3}J=3.1 Hz, 2H, H-10b), 2.16 (dqq, ^{3}J=8.1 Hz, ^{3}J=6.7 Hz, ^{3}J=6.7 Hz, 2H, H-4), 1.19 (d, ^{3}J=6.6 Hz, 6H, H-9), 1.02 (d, ^{3}J=6.7 Hz, 6H, H-5/6), 0.90 (d, ^{3}J=6.7 Hz, 6H, H-5/6).

^{13}C-NMR (150.9 MHz, 298K, $CDCl_3$): δ= 173.85 (C-3), 139.25 (C-13), 129.18 (C-15), 128.69 (C-14), 127.53 (C-16), 71.77 (C-2), 58.46 (C-12), 54.08 (C-10), 45.04 (C-8), 28.06 (C-4), 22.20 (C-5/6), 20.06 (C-5/6), 18.44 (C-9).

(2*S*,5*S*,8*S*,11*S*)-1,7-dibenzyl-2,8-diisopropyl-5,11-dimethyl-1,4,7,10-tetraazacyclododecane (21)



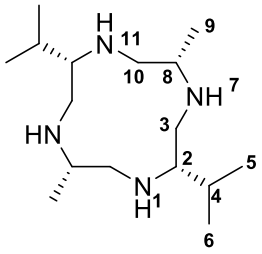
(3*S*,6*S*,9*S*,12*S*)-4,10-Dibenzyl-3,9-diisopropyl-6,12-dimethyl-1,4,7,10-tetraaza-cyclododecane-2,8-dione (**18**) (1.49 g, 3.02 mmol, 1.0 eq.) was dissolved in dichloromethane (50 mL) and was cooled to 0-5 °C. Trimethylchlorosilane (2.2 mL, 17.5 mmol, 5.8 eq.) was added and the solution was stirred for 1 h at 0-5 °C. A suspension with $LiAlH_4$ (0.49 g, 12.9 mmol, 4.3 eq.) and THF (10 mL) was prepared under inert conditions and added dropwise to the reaction mixture at 0-5 °C. After 3 h the excess of $LiAlH_4$ was quenched with aqueous potassium hydroxide (1 M, 2 mL). The suspension was dried over sodium sulphate, filtered and the filter cake was washed with dichloromethane (5x 20 mL). The filtrate was evaporated to dryness and was purified by flash column chromatography (SiO_2, ethyl acetate 1% NEt_3) yielding a white solid (1.29 g, 2.77 mmol, 91.9%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{30}H_{49}N_4$ m/z=465.3952, found m/z=465.3958.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 7.5-7.1 (m, 10H, H-14, H-15, H-17), 4.03 (d, ^{2}J=11.5 Hz, 2H, H-12a), 3.16 (d, 2H, ^{2}J=11.5 Hz, 2H, H-12b), 2.86-2.74 (m, 4H, H-3a, H-8), 2.65-2.59 (m, 4H, H-10a, H-2), 2.53 (bs, 2H, H-3b), 2.34-2.25 (m, 2H, H-10b), 2.20-2.03 (m, 2H, H-4), 1.00 (d, ^{3}J=6.6 Hz, 6H, H-5/6), 0.92 (d, ^{3}J=6.7 Hz, 6H, H-5/6), 0.87 (bs, 6H, H-9).

^{13}C-NMR (125.75 MHz, 298K, $CDCl_3$): δ= 140.30 (C-13), 129.24 (C-15), 128.49 (C-14), 127.30 (C-16), 59.22 (C-2), 56.62 (C-10), 53.15 (C-12), 45.74 (C-8), 41.46 (C-3), 24.43 (C-4), 24.18 (C-5/6), 19.34 (C-5/6), 18.82 (C-9).

(2*S*,5*S*,8*S*,11*S*)-2,8-diisopropyl-5,11-dimethyl-1,4,7,10-tetraazacyclododecane (M2P2-cyclen)



(2*S*,5*S*,8*S*,11*S*)-1,7-Dibenzyl-2,8-diisopropyl-5,11-dimethyl-1,4,7,10-tetraazacyclododecane (**21**) (197 mg, 0.42 mmol, 1.0 eq.) was dissolved in ethanol (30 mL) and ethyl acetate (3 mL). Palladium on activated charcoal (101 mg, 10% Pd) and ammonium formate (612 mg, 9.71 mmol, 23 eq.) were added and the resulting suspension was heated to reflux for 16 h. The suspension was cooled to 20-25°C, filtered over celite and washed with methanol (3 x 20 mL). The solvent was removed under reduced pressure yielding a white solid (118 mg, 0.41 mmol, 98.2%).

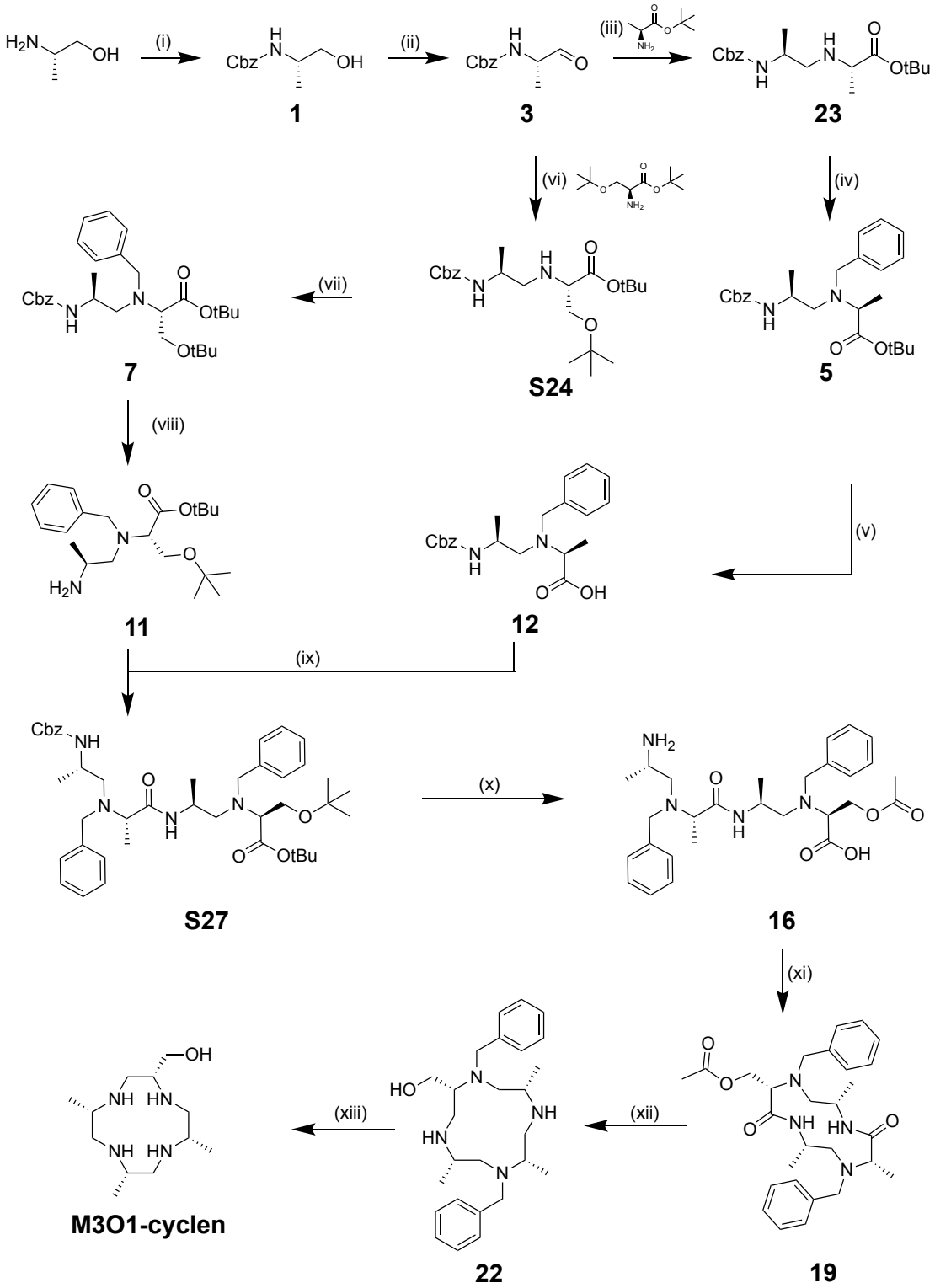
HR-ESI-MS: calcd. for $[M+H]^+$ $C_{16}H_{37}N_4$ m/z=285.3013, found m/z=285.3013.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 2.70 (dd, ^{2}J=13.1 Hz, ^{3}J=2.8 Hz, 2H, H-10a), 2.64 (dd, ^{2}J=13.0 Hz, ^{3}J=1.9 Hz, 2H, H-3a), 2.64-2.59 (m, 2H, H-8), 2.46-2.35 (m, 6H, H-3b, H-10b, H-2), 1.94-1.86 (m, 2H, H-4), 0.94 (d, ^{3}J=7.0 Hz, 6H, H-5/6), 0.91 (d, ^{3}J=6.3 Hz, 6H, H-9), 0.85 (d, ^{3}J=7.0 Hz, 6H, H-5/6).

^{13}C-NMR (125.75 MHz, 298K, $CDCl_3$): δ= 57.13 (C-2), 52.60 (C-10), 47.64 (C-8), 44.98 (C-3), 28.13 (C-4), 20.29 (C-5/6), 18.16 (C-9), 16.62 (C-5/6).

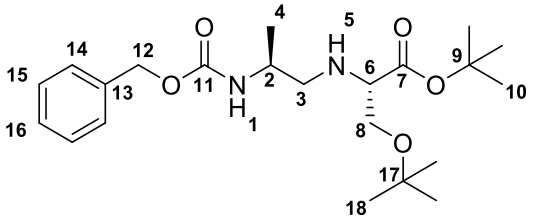
$[\alpha_D^{20}]$ + 65.4° (c 1.00, $CHCl_3$).

SYNTHESIS OF M3O1-CYCLEN



Scheme S3: Synthetic route towards M3O1-cyclen. Reaction conditions. i) Cbz-Cl, Na_2CO_3, H_2O, EtOAc, 20-25 °C, 1h; ii) IBX, DMSO, EtOAc, RF, 3.5 h; iii) $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 16 h; iv) BnBr, K_2CO_3, MeCN, 50 °C, 16 h; v) HCl in dioxane, 40 °C, 18 h; vi) $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 16 h; vii) BnBr, K_2CO_3, MeCN, 40 °C, 18 h; viii) 5% Pd/$BaSO_4$, MeOH, 20-25 °C, 24 h; ix) HATU, DIPEA, MeCN, 20-25 °C, 2 h; x) HBr in AcOH 16 wt. %, 40 °C, 30 min; xi) HATU, DIPEA, MeCN, 20-25 °C, 20 min; xii) TMS-Cl, $LiAlH_4$, THF/CH_2Cl_2, 0-5 °C → 20-25 °C; xiii) ammonium formate, Pd/C, EtOH, RF, 16 h.

***tert*-Butyl *N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*O*-(*tert*-butyl)-*L*-serinate (S24).**



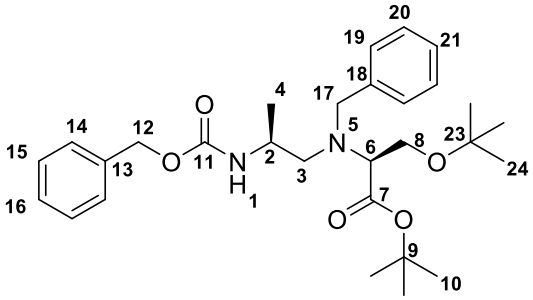
Benzyl (*S*)-(1-oxopropan-2-yl)carbamate (**3**) (2.60 g, 12.5 mmol, 1.08 eq.) was dissolved in dichloromethane (20 mL). To this solution *tert*-Butyl *O*-(*tert*-butyl)-*L*-serinate (2.52 g, 12.5 mmol, 1.0 eq.) was added. The solution was stirred at 20-25 °C for 5 min. followed by the addition of sodium triacetoxyborohydride (10.9 g, 51.4 mmol, 4.4 eq.). The reaction mixture was stirred at 20-25 °C for 16 h. The excess of sodium triacetoxyborohydride was quenched with aqueous saturated sodium hydrogencarbonate (50 mL) and the pH adjusted to >9 by addition of triethylamine (5 mL). The layers were separated and the organic layer was washed with water (30 mL) and dried with sodium sulphate. The organic layer was evaporated to dryness yielding a slightly yellowish oil (4.61 g, 11.3 mmol, 97.3%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{22}H_{37}N_2O_5$ m/z=409.2697, found m/z= 409.2700.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ=7.40-7.27 (m, 5H, H-14,H-15, H-16), 5.23 (bs, 1H, H-1), 5.08 (s, 2H, H-12), 3.73 (qdd, ^{3}J=6.7 Hz, ^{3}J=5.7 Hz, ^{3}J=5.2 Hz, 1H, H-2), 3.52 (dd, ^{2}J=8.3 Hz, ^{3}J=5.4 Hz, 1H, H-8a), 3.49 (dd, ^{2}J=8.3 Hz, ^{3}J=4.7 Hz, 1H, H-8b), 3.24 (dd, ^{3}J=5.4 Hz, ^{3}J=4.7 Hz, 1H, H-6), 2.75 (dd, ^{2}J=12.6 Hz, ^{3}J=5.2 Hz, 1H, H-3a), 2.53 (dd, ^{2}J=12.6 Hz, ^{3}J=5.7 Hz, 1H, H-3b), 1.45 (s, 9H, H-10), 1.17 (d, ^{3}J=6.7 Hz, 3H, H-4), 1.15 (s, 9H, H-18).

^{13}C-NMR (100.61 MHz, 298K, $CDCl_3$): δ=172.52 (C-7), 156.46 (C-11), 136.88 (C-13), 128.57 (C-15), 128.17 (C-14), 128.08 (C-16), 81.19 (C-9), 73.13 (C-17), 66.53 (C-12), 62.99 (C-8), 62.70 (C-6), 52.73 (C-3), 47.33 (C-2), 28.25 (C-10), 27.51 (C-18), 18.99 (C-4).

***tert*-Butyl *N*-benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*O*-(*tert*-butyl)-*L*-serinate (7).**



tert-Butyl *N*-((*S*)-2-(((benzyloxy) carbonyl)amino)propyl)-O-(*tert*-butyl)-*L*-serinate (**S24**) (3.58 g, 8.76 mmol, 1.0 eq) and potassium carbonate (1.37 g, 9.91 mmol, 1.13 eq.) were suspended in acetonitrile (35 mL). Over a period of 2 min. benzyl bromide (1.30 mL, 10.9 mmol, 1.24 eq) was added. The reaction mixture was heated to 40 °C and stirred for 18 h under an argon atmosphere. The excess of benzyl bromide was quenched with NEt_3 (10 mL). The suspension was heated to 50 °C and stirred for 40 min. before cooled 20-25 °C. The reaction mixture was filtered and the filter cake was washed with acetonitrile (20 mL). The filtrate was then evaporated to dryness and the crude oil was purified by flash column chromatography (SiO_2, cyclohexane / ethyl acetate (8:2) 1% NEt_3) yielding a colorless oil (2.99 g, 5.99 mmol, 68.4%, mixture of diastereomers <10%).

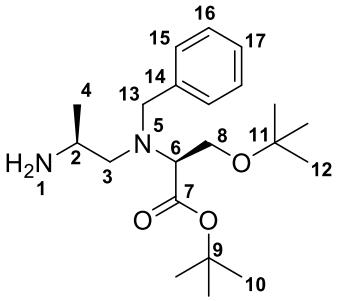
HR-ESI-MS: calcd. for $[M+H]^+$ $C_{29}H_{43}N_2O_5$ m/z=499.3166, found m/z= 499.3173.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ=7.41-7.17 (m, 10H, H-14, H-15, H-16, H-19, H-20, H-21), 5.79 (bs, 1H, H-2), 5.11 (d, ^{2}J=12.3 Hz, 1H, H-12a), 5.06 (d, ^{2}J=12.3 Hz, 1H, H-12b), 3.89 (d, ^{2}J=14.4 Hz, 1H, H-17a), 3.83 (d, ^{2}J=14.4 Hz, 1H, H-17b), 3.73-3.64 (m, 1H, H-2), 3.64 (dd, ^{2}J=9.4 Hz, ^{3}J=5.6 Hz, 1H, H-8a), 3.57 (dd, ^{2}J=9.4 Hz, ^{3}J=7.1 Hz, 1H, H-8b), 3.39 (dd, ^{3}J=7.1 Hz, ^{3}J=5.6

Hz, 1H, H-6), 2.82 (dd, ^{2}J=13.3 Hz, ^{3}J=4.9 Hz, 1H, H-3a), 2.73 (dd, ^{2}J=13.3 Hz, ^{3}J=7.1 Hz, 1H, H-3b), 1.46 (s, 9H, H-24), 1.16 (d, ^{3}J=7.6 Hz, 3H, H-4), 1.15 (s, 9H, H-10).

^{13}C-NMR (125.76 MHz, 298K, $CDCl_3$): δ= 171.22 (C-7), 156.34 (C-11), 139.69 (C-18), 137.04 (C-13), 128.59 (C-19), 128.38 (C-20), 128.22 (C-15), 128.01 (C-14), 127.82 (C-21), 126.92 (C-16), 81.18 (C-23), 73.24 (C-9), 66.18 (C-12), 63.59 (C-6), 60.32 (C-8), 57.03 (C-17), 56.49 (C-3), 46.11 (C-2), 28.22 (C-24), 27.34 (C-10), 19.28 (C-4).

***tert*-Butyl *N*-((*S*)-2-aminopropyl)-*N*-benzyl-*O*-(*tert*-butyl)-*L*-serinate (11)**



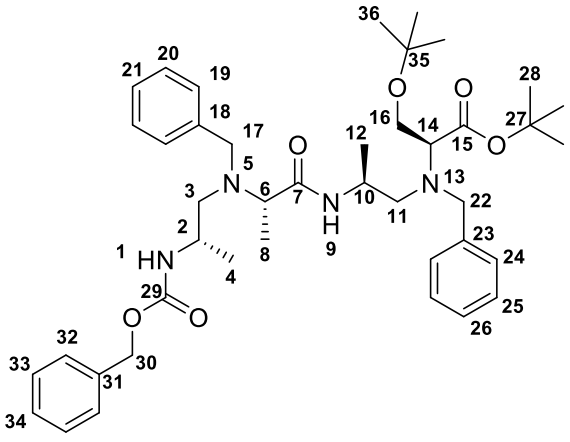
tert-Butyl *N*-benzyl -*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-O-(*tert*-butyl)-*L*-serinate (**7**) (2.99 g, 6.00 mmol, 1.0 eq.) was dissolved in methanol (30 mL). Palladium on barium sulphate (50 mg, 5% Pd / $BaSO_4$) was added and the reaction flask was flushed with nitrogen. Then hydrogen was bubbled through the solution for 5 minutes and the reaction mixture was left stirring under a hydrogen atmosphere for 24 h. The suspension was filtered over celite and washed with methanol (3 x 50 mL). The filtrate was evaporated to dryness yielding a slightly yellowish oil (2.02 g, 5.53 mmol, 92.4%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{21}H_{36}N_2O_3$ m/z=365.2799, found m/z= 365.2803.

^{1}H-NMR (500.13 MHz, 298K, CD_3CN): δ= 7.38-7.25 (m, 5H, H-15, H-16, H-17), 3.90 (d, ^{2}J=13.8 Hz, 1H, H-13a), 3.76 (d, ^{2}J=13.8 Hz, 1H, H-13b), 3.63 (dd, ^{2}J=10.5 Hz, ^{3}J=5.1 Hz, 1H, H-8a), 3.55 (dd, ^{2}J=10.5 Hz, ^{3}J=9.4 Hz, 1H, H-8b), 3.42-3.34 (m, 1H, H-2), 3.37 (dd, ^{3}J=5.1 Hz, ^{3}J=4.2 Hz, 1H, H-6), 2.95 (dd, ^{2}J=14.3 Hz, ^{3}J=3.4 Hz, 1H, H-3a), 2.73 (dd, ^{2}J=14.3 Hz, ^{3}J=11.7 Hz, 1H, H-3b), 1.48 (s, 9H, H-10), 1.21 (d, ^{3}J=6.6 Hz, 3H, H-4), 1.15 (s, 9H, H-12).

^{13}C-NMR (125.76 MHz, 298K, CD_3CN): δ= 171.17 (C-7), 139.83 (C-14), 130.03 (C-16), 129.45 (C-15), 128.33 (C-17), 82.63 (C-9), 75.25 (C-11), 63.36 (C-6), 60.02 (C-8), 57.32 (C-13), 54.53 (C-3), 47.57 (C-2), 28.43 (C-10), 27.57 (C-12), 15.77 (C-4).

***tert*-Butyl (5S,8S,11S,14S)-7,13-dibenzyl-14-(*tert*-butoxymethyl)-5,8,11-trimethyl-3,9-dioxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (S27)**



N-benzyl-*N*-((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-alanine (**12**) hydrochloride (2.16 g, 5.32 mmol, 1.0 eq.), *tert*-butyl *N*-((*S*)-2-aminopropyl)-*N*-benzyl-O-(*tert*-butyl)-*L*-serinate (**11**) (1.94 g, 5.32 mmol, 1.00 eq.) and DIPEA (2.71 mL, 16.4 mmol, 3.1 eq.)

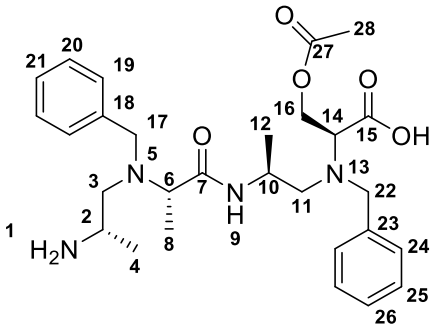
were dissolved in acetonitrile (30 mL). To this solution HATU (2.45 g, 6.44 mmol, 1.2 eq.) was added. The reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure and the crude oil was purified by flash column chromatography (SiO_2, ethyl acetate / cyclohexane (7:3) 1% NEt_3) yielding a yellowish oil (3.35 g, 4.67 mmol, 87.8%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{42}H_{61}N_4O_6$ m/z=717.4586, found m/z= 717.4588.

^{1}H-NMR (500.13 MHz, 298K, DMSO-d_6): δ= 7.40-7.12 (m, 15H, H-19, H-20, H-21, H-24, H-25, H-26, H-32, H-33, H-34), 5.10 (d, ^{2}J=12.6 Hz, 1H, H-30a), 4.92 (d, ^{2}J=12.6 Hz, 1H, H-30b), 4.75 (d, ^{3}J=6.8 Hz, 1H, H-1), 4.02 (ddq, ^{3}J=7.2 HZ, ^{3}J=6.9 Hz, ^{3}J=6.5, 1H, H-10), 3.92 (d, ^{2}J=14.7 Hz, 1H, H-22a), 3.83-3.78 (m, 1H, H-2), 3.76 (d, ^{2}J=14.7 Hz, 1H, H-22b), 3.71 (d, ^{2}J=13.7 Hz, 1H, H-17a), 3.64 (dd, ^{2}J=8.6 Hz, ^{3}J=5.4 Hz, 1H, H-16a), 3.51 (dd, ^{2}J=8.6 Hz, ^{3}J=5.7 Hz, 1H, H-16b), 3.40 (d, ^{2}J=13.7 Hz, 1H, H-17b), 3.35 (dd, ^{3}J=5.7 Hz, ^{3}J=5.4 Hz, 1H, H-14), 2.79 (dd, ^{2}J=13.3 Hz, ^{3}J=6.9 Hz, 1H, H-11a), 2.75 (dd, ^{2}J=13.3 Hz, ^{3}J=7.2 Hz, 1H, H-11b), 2.50 (dd, ^{2}J=13.5 Hz, ^{3}J=3.7 Hz, 1H, H-3a), 2.32 (dd, ^{2}J=13.5 Hz, ^{3}J=10.5 Hz, 1H, H-3b), 1.44 (s, 9H, H-28), 1.21 (d, ^{3}J=6.9 Hz, 3H, H-8), 1.17 (d, ^{3}J=6.5 Hz, 3H, H-12), 1.13 (s, 9H, H-36), 1.05 (d, ^{3}J=7.3 Hz, 3H, H-4).

^{13}C-NMR (125.77 MHz, 298K, DMSO-d_6): δ= 173.03 (C-7), 171.42 (C-15), 156.45 (C-29), 140.20 (C-23), 139.37 (C-18), 136.84 (C-31), 129.05 (C-19), 128.68 (C-24), 128.58 (C-arom.), 128.43 (C-arom.), 128.28 (C-arom.), 128.23 (C-32), 128.14 (C-arom.), 127.22 (C-arom.), 126.85 (C-arom.), 80.95 (C-27), 72.99 (C-35), 66.62 (C-30), 63.13 (C-14), 58.54 (C-6), 57.24 (C-22), 57.08 (C-11), 56.42 (C-3), 54.99 (C-17), 45.25 (C-2), 44.68 (C-10), 28.41 (C-28), 27.51 (C-36), 19.50 (C-4), 19.18 (C-12), 8.63 (C-8).

***O*-acetyl-*N*-((*S*)-2-((*S*)-2-(((*S*)-2-aminopropyl)(benzyl)amino)propanamido)propyl)-*N*-benzyl-*L*-serine (16).**



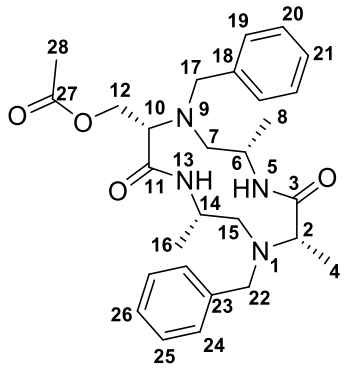
tert-Butyl (5*S*,8*S*,11*S*,14*S*)-7,13-dibenzyl-14-(*tert*-butoxymethyl)-5,8,11-trimethyl-3,9-dioxo-1-phenyl-2-oxa-4,7,10,13-tetra-azapentadecan-15-oate (**S27**) (1.04 g, 1.45 mmol, 1.0 eq) was dissolved in acetic acid (10 mL) and hydrobromic acid solution (33 wt.% in acetic acid, 10 mL). The solution was stirred at 40 °C for 30 minutes and evaporated to dryness. This oil was further suspended in acetonitrile (10 mL) and hydrochloric acid (0.5 mL, 37% aq.). This mixture was again evaporated to dryness. This procedure was repeated three times to remove residual acetic acid from the product. Finally, methanol (10 mL) was added and the solvent was removed under reduced pressure yielding a brownish foam. This foam was extensively dried under high vacuum at 40 °C for 2 days. The product (1.12 g) is obtained as a mixture of HCl and HBr salt with minimal acetate content and was further used without additional purification.

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{28}H_{41}N_4O_5$ m/z=513.3071, found m/z= 513.3071.

^{1}H-NMR (500.13 MHz, 298K, DMSO-d_6): δ= 7.40-7.21 (m, 10H, H-19, H-20, H-21, H-24, H-25, H-26), 4.23 (dd, ^{2}J=11.5 Hz, ^{3}J=5.7 Hz, 1H, H-16a), 4.11 (dd, ^{2}J=11.5 Hz, ^{3}J=7.8 Hz, 1H, H-16b), 3.92-3.82 (m, 1H, H-10), 3.87 (d, ^{2}J=14.1 Hz, 1H, H-22a), 3.72 (d, ^{2}J=14.1 Hz, 1H, H-22b), 3.68-3.63 (m, 2H, H-17), 3.50 (dd, ^{3}J=7.8 Hz, ^{3}J=5.7 Hz, 1H, H-14), 3.28 (q, ^{3}J=7.0 Hz, 1H, H-6), 3.22-3.13 (m, 1H, H-2), 2.69-2.59 (m, 2H, H-3), 2.63 (dd, ^{2}J=12.5 Hz, ^{3}J=4.9 Hz, 1H, H-11a), 2.46 (dd, ^{2}J=12.5 Hz, ^{3}J=9.2 Hz, 1H, H-11b), 1.97 (s, 3H, H-28), 1.13 (d, ^{3}J=7.0 Hz, 3H, H-8), 1.10 (d, ^{3}J=6.5 Hz, 3H, H-4), 1.02 (d, ^{3}J=6.6 Hz, 3H, H-12).

^{13}C-NMR (125.77 MHz, 298K, DMSO-d_6): δ= 172.49 (C-7), 171.55 (C-15), 170.02 (C-27), 139.29 (C-23), 138.85 (C-18), 128.35 (C-arom.), 128.47 (C-arom.), 128.31 (C-arom.), 128.15 (C-arom.), 127.15 (C-arom.), 127.00 (C- arom.), 62.09 (C-16), 60.41 (C-14), 57.57 (C-6), 56.03 (C-11), 55.87 (C-22), 55.70 (C-17), 53.82 (C-3), 45.26 (C-2), 43.27 (C-10), 20.01 (C-28), 18.28 (C-12), 16.45 (C-4), 12.76 (C-8).

((2*S*,5*S*,8*S*,11*S*)-1,7-dibenzyl-5,8,11-trimethyl-3,9-dioxo-1,4,7,10-tetraazacyclododecan-2-yl)methyl acetate (19).



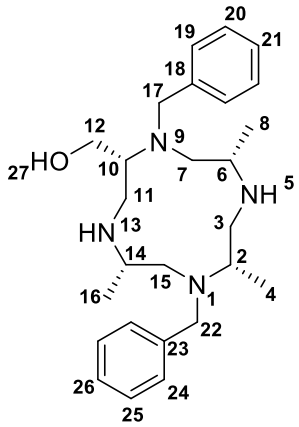
O-Acetyl-*N*-((*S*)-2-((*S*)-2-(((*S*)-2-aminopropyl)(benzyl)amino)propanamido)propyl)-*N*-benzyl-*L*-serine (**16**) salt (1.07 g, ~1.4 mmol, 1.0 eq), DIPEA (1.42 mL, 8.60 mmol, 6.1 eq.) were dissolved in acetonitrile (1 L). Then HATU (0.90 g, 2.37 mmol, 1.7 eq.) was added to the solution. After 1h the solvent was removed under reduced pressure and the crude oil was purified by flash column chromatography (SiO_2, ethyl acetate 1% NEt_3) yielding a yellowish solid (318 mg, 0.64 mmol, 44.8% yield calculate for 2 steps starting from **S27**).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{28}H_{39}N_4O_4$ m/z=495.2966, found m/z= 495.2971.

^{1}H-NMR (400.13 MHz, 298K, DMSO-d_6): δ= 7.90 (d, ^{3}J=5.3 Hz, 1H, H-13), 7.68 (d, ^{3}J=4.1 Hz, 1H, H-5), 7.47-7.43 (m, 2H, H-25), 7.43-7.38 (m, 2H, H-19), 7.37-7.24 (m, 6H, H-24, H-26, H-20, H-21), 4.38 (dd, ^{2}J=11.7 Hz, ^{3}J=5.9 Hz, 1H, H-12a), 4.32 (dd, ^{2}J=11.7 Hz, ^{3}J=7.5 Hz, 1H, H-12b), 4.00 (d, ^{2}J=13.4 Hz, 1H, H-17a), 3.93 (d, ^{2}J=13.4 Hz, 1H, H-22a), 3.80 (d, ^{2}J=13.4 Hz, 1H, H-17b), 3.53 (d, ^{2}J=13.4 Hz, 1H, H-22b), 3.53-3.45 (m, 1H, H-14), 3.51 (dd, ^{3}J=7.1 Hz, ^{3}J=5.9 Hz, 1H, H-10), 3.24-3.15 (m, 1H, H-6), 3.16 (q, ^{3}J=7.1 Hz, 1H, H-2), 2.94 (dd, ^{2}J=13.3 Hz, ^{3}J=11.3 Hz, 1H, H-7a), 2.78 (dd, ^{2}J=13.1 Hz, ^{3}J=11.3 Hz, 1H, H-15a), 2.48 (dd, ^{2}J=13.3 Hz, ^{3}J=2.9 Hz, 1H, H-7b), 2.29 (dd, ^{2}J=13.1 Hz, ^{3}J=2.5 Hz, 1H, H-15b), 2.04 (s, 3H, H-28), 1.18 (d, ^{3}J=6.5 Hz, 3H, H-16), 1.11 (d, ^{3}J=6.4 Hz, 3H, H-8), 1.04 (d, ^{3}J=7.1 Hz, 3H, H-4).

^{13}C-NMR (100.61 MHz, 298K, DMSO-d_6): δ= 172.17 (C-3), 170.21 (C-27), 169.31 (C-11), 139.04 (C-23), 138.99 (C-18), 129.21 (C-24), 129.14 (C-19), 128.23 (C-25), 128.18 (C-20), 127.24 (C-26), 127.17 (C-21), 63.22 (C-10), 60.38 (C-12), 59.18 (C-2), 58.32 (C-17), 56.45 (C-22), 55.14 (C-7), 54.80 (C-15), 44.13 (C-14), 43.99 (C-6), 20.79 (C-28), 17.65 (C-16), 17.59 (C-8), 8.44 (C-4).

((2*R*,5*S*,8*S*,11*S*)-1,7-dibenzyl-5,8,11-trimethyl-1,4,7,10-tetraazacyclododecan-2-yl)methanol (22).



((2*S*,5*S*,8*S*,11*S*)-1,7-dibenzyl-5,8,11-trimethyl-3,9-dioxo-1,4,7,10-tetraazacyclododecan-2-yl)methyl acetate (**19**) (152 mg, 0.30 mmol, 1.0 eq.) was dissolved in dichloromethane (15 mL) and cooled to 0-5 °C. To this solution trimethylchlorosilane (0.25 mL, 1.98 mmol, 6.46 eq.) was added and stirred for 30 minutes under an argon atmosphere. To the reaction mixture lithium aluminium hydride (2M in THF, 1.00 mL, 2.01 mmol, 6.54 eq.) was added dropwise. After 3 h additional $LiAlH_4$ in THF (2 M, 1.0 mL, 2.01 mmol, 6.54 eq.) was added dropwise and the reaction mixture was stirred at 20-25 °C for 24 h. The excess of $LiAlH_4$ was

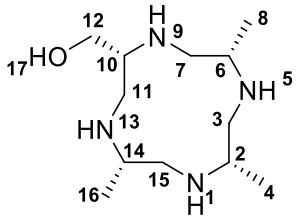
quenched with KOH (1 M, aq., 1 mL). The suspension was dried with sodium sulphate, filtered and the filter cake was washed with dichloromethane (3 x 20 mL). The filtrate was evaporated to dryness yielding a slightly yellowish solid (123 mg, 0.28 mmol, 94.1%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{26}H_{41}N_4O$ m/z=425.3275, found m/z= 425.3279.

^{1}H-NMR (600.13 MHz, 298K, DMSO-d_6): δ= 3.95 (d, ^{2}J=12.4 Hz, 1H), 3.82-3.73 (m, 2H), 3.43 (dd, ^{2}J=12.2 Hz, ^{3}J=6.7 Hz, 1H), 3.25 (d, ^{2}J=11.1 Hz, 1H), 3.06 (bs, 1H), 3.01 (d, ^{2}J=11.2 Hz, 1H), 2.93 (bs, 1H), 2.89-2.59 (m, 6H), 2.47 (bs, 1H), 2.41 (bs, 1H), 2.26 (bs, 1H), 2.13 (bs, 1H), 0.90 (d, ^{3}J=6.6 Hz, 3H), 0.82 (bs, 6H).

^{13}C-NMR (150.9 MHz, 298K, DMSO-d_6): δ= 141.03 (C-arom.), 140.90 (C-arom.), 129.75 (C-arom.), 129.49 (C-arom.), 128.59 (C-arom.), 128.58 (C-arom.), 127.25 (C-arom.), 60.06 (C-CH), 58.00 (C-CH2), 57.21 (C-CH), 56.56 (C-CH_2), 53.10 (C-CH_2), 51.42 (C-CH_2), 49.50 (C-CH), 47.47 (C-CH_2), 46.48 (C-CH), 46.36 (C-CH), 44.49 (C-CH_2), 18.09 (C-CH_3), 17.98 (C-CH_3), 9.91 (C-CH_3).

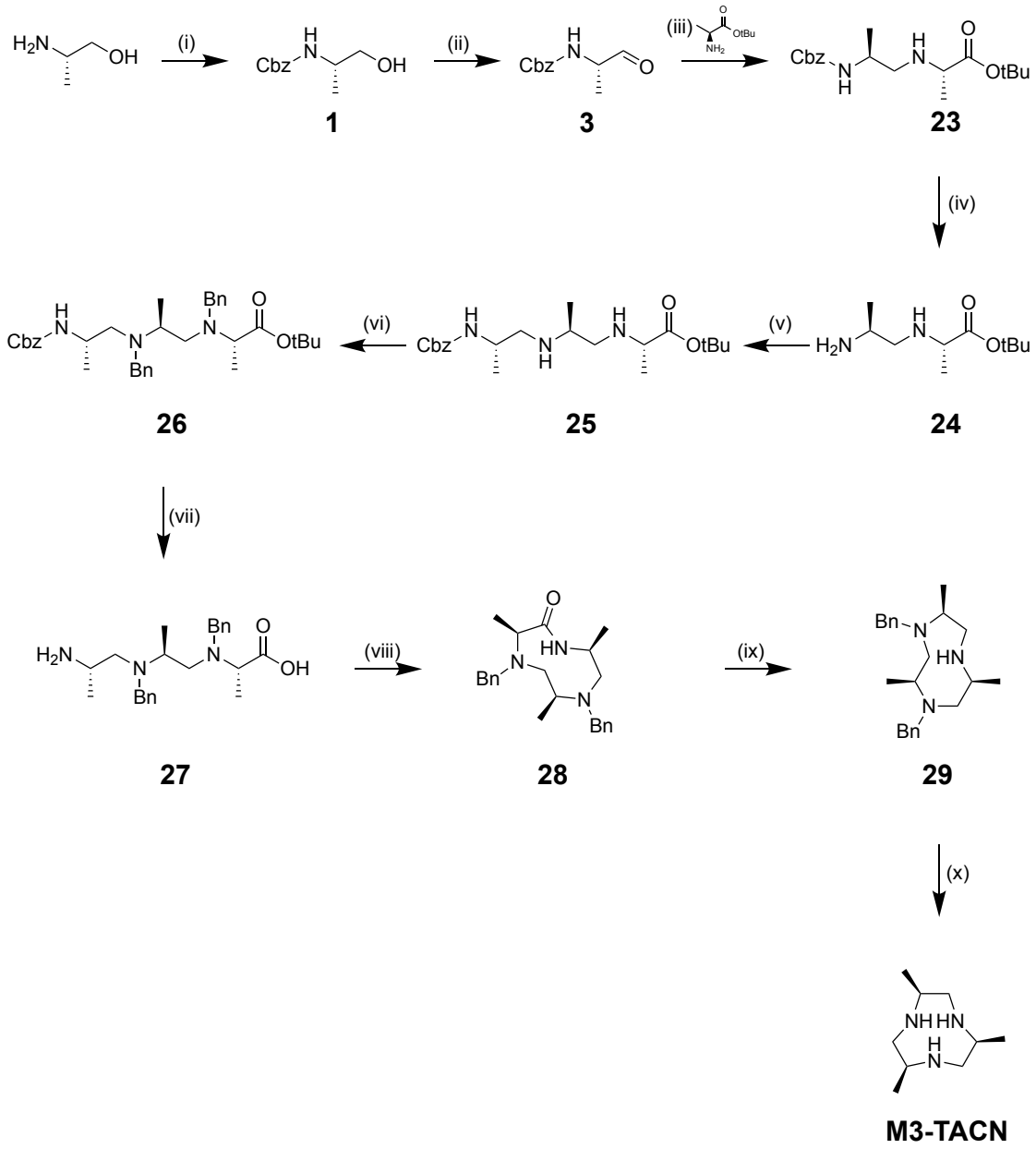
((2*R*,5*S*,8*S*,11*S*)-5,8,11-trimethyl-1,4,7,10-tetraazacyclododecan-2-yl)methanol (M3O1-cyclen).



((2*R*,5*S*,8*S*,11*S*)-1,7-dibenzyl-5,8,11-trimethyl-1,4,7,10-tetraazacyclododecan-2-yl)methanol (**22**) (65 mg, 0.15 mmol, 1.0 eq.) was dissolved in methanol (2 mL) and trifluoroacetic acid (0.1 mL). Palladium on activated charcoal (100 mg, moistened with water, 10% Pd) was added and the suspension was hydrogenated at room temperature and 90 bar H_2 pressure for 17 h. The suspension was filtered. The filtrate was evaporated to dryness yielding an off-white solid (32 mg, 0.13 mmol, 85.6%).

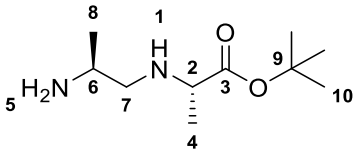
HR-ESI-MS: calcd. for $[M+H]^+$ $C_{12}H_{29}N_4O$ m/z=245.2336, found m/z= 245.2335.

SYNTHESIS OF M3-TACN



Scheme S4: Synthetic route towards M3-TACN. Reaction conditions: i) Cbz-Cl, Na_2CO_3, H_2O, EtOAc, 20-25 °C, 1 h; ii) IBX, DMSO, EtOAc, RF, 3.5 h; iii) $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 16 h; iv) Pd/C, MeOH, 20-25°C, H_2, 4 h; v) **3**, $NaBH(OAc)_3$, CH_2Cl_2, 20-25 °C, 16 h; vi) BnBr, K_2CO_3, MeCN, 20-25 °C, 16 h; vii) HBr in AcOH 16 wt%, 40 °C, 30 min; viii) HATU, DIPEA, MeCN, 20-25 °C, 30 min; ix) TMS-Cl, $LiAlH_4$, THF/CH_2Cl_2, 0-5 °C → 20-25 °C; x) ammonium formate, Pd/C, EtOH, RF, 16 h.

***tert*-Butyl ((S)-2-aminopropyl)-*L*-alaninate (24)**



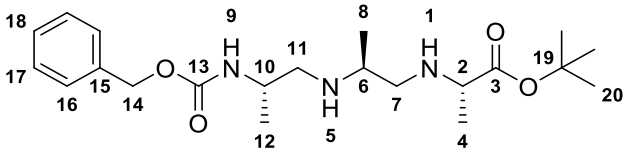
tert-Butyl ((*S*)-2-(((benzyloxy)carbonyl)amino)propyl)-*L*-alaninate (**23**) (15.5 g, 46.0 mmol, 1.0 eq.) was dissolved in methanol (400 mL) and palladium on activated charcoal (700 mg, 10% Pd) was added. The suspension was stirred at 20-25°C under an atmosphere of hydrogen for 4 h. The suspension was filtered over celite and the filter cake was washed with methanol (100 mL). The filtrate was evaporated to dryness yielding a yellowish liquid (6.78 g, 33.5 mmol, 72.9%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{10}H_{23}N_2O_2$ m/z=203.1754, found m/z= 203.1753.

^{1}H-NMR (250.13 MHz, 298K, DMSO-d_6): δ= 3.02 (q, ^3J=7,0 Hz, 1H, H-2), 2,77 (ddq, ^3J =8.4 Hz, ^3J =4.2 Hz, ^3J =6.4 Hz, 1H, H-6), 2.50 (dd, ^2J =11.4 Hz, ^3J =4.2 Hz, 1H, H-7a), 2.05 (dd, ^2J =11.4 Hz, ^3J =8.4 Hz, 1H, H-7b), 1.32 (s, 9H, H-10), 1.10 (d, ^3J =7.0 Hz, 3H, H-4), 0.90 (d, ^3J =6.4 Hz, 3H, H-8).

^{13}C-NMR (62.9 MHz, 298K, DMSO-d_6): δ= 175.2 (C-3), 80.7 (C-9), 57.6 (C-2), 56.4 (C-7), 46.9 (C-6), 28.0 (C-10), 21.3 (C-8), 19.1 (C-4).

***tert*-Butyl ((S)-2-(((S)-2-(((benzyloxy)carbonyl)amino)propyl)amino)propyl)-*L*-alaninate (25)**



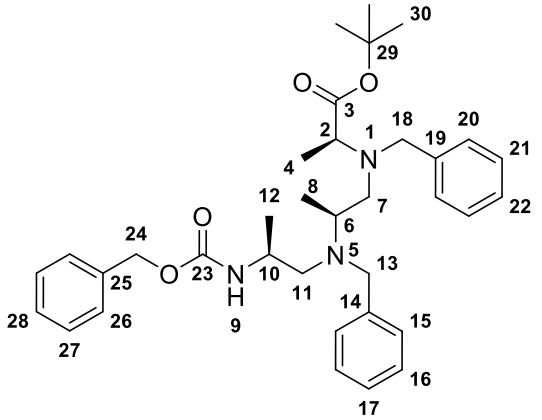
tert-Butyl ((S)-2-aminopropyl)-*L*-alaninate **(24)** (6.78 g, 33.5 mmol, 1.0 eq.) was dissolved in dichloromethane (100 mL). To this solution benzyl (*S*)-(1-oxopropan-2-yl)carbamate (**S2**) (6.94 g, 33.5 mmol, 1.0 eq.) was added. The solution was stirred at 20-25 °C for 5 min. followed by the addition of sodium triacetoxyborohydride (21.3 g, 101 mmol, 3.0 eq.). The reaction mixture was stirred at 20-25 °C for 16 h. The excess of sodium triacetoxyborohydride was quenched with aqueous saturated sodium hydrogen carbonate (100 mL) and the pH adjusted to >9 by addition of triethylamine (35 mL). The layers were separated and the organic layer was washed with water (100 mL) and dried with sodium sulphate. The organic layer was evaporated to dryness yielding a yellowish oil (12.8 g, 32.5 mmol, 97.1%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{21}H_{36}N_3O_4$ m/z=394.2700, found m/z= 394.2704.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 7.38-7.27 (m, 5H, H-16, H-17, H-18), 5.20 (bs, 1H, H-9), 5.11 (d, ^2J =12.1 Hz, 1H, H-14a), 5.06 (d, ^2J =12.1 Hz, 1H, H-14b), 3.82-3.72 (m, 1H, H-10), 3.14 (q, ^3J =7.0 Hz, 1H, H-2), 2.68-2.58 (m, 4H, H-6, H-7a, H-11), 2.30 (dd, ^2J =11.3 Hz, ^3J =7.8 Hz, 1H, H-7b), 1.45 (s, 9H, H-20), 1.22 (d, ^3J =7.0 Hz, 3H, H-4), 1.17 (d, ^3J =6.4 Hz, 3H, H-12), 1.00 (d, ^3J =6.2Hz, 3H, H-8).

^{13}C-NMR (125.77 MHz, 298K, $CDCl_3$): δ= 175.3 (C-3), 156.1 (C-13), 136.7 (C-15), 128.5 (C-17), 128.1 (C-18), 128.0 (C-16), 80.8 (C-19), 66.5 (C-14), 57.6 (C-2), 53.6 (C-7), 53.0 (C-6), 51.9 (C-11), 47.0 (C-10), 28.1 (C-20), 19.1 (C-12), 19.1 (C-4), 18.7 (C-8).

***tert*-Butyl (5S,8S,11S)-7,10-dibenzyl-5,8,11-trimethyl-3-oxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (26)**



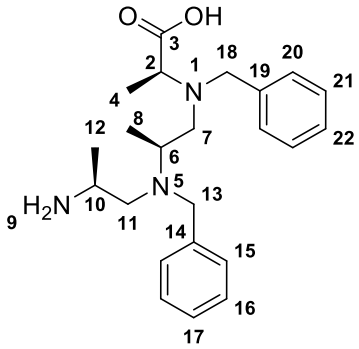
tert-Butyl ((S)-2-(((S)-2-(((benzyloxy)carbonyl)amino)propyl)amino)propyl)-*L*-alaninate (**25**) (12.8 g, 32.5 mmol, 1.0 eq.) was dissolved in acetonitrile (150 mL) and potassium carbonate (18.5 g, 134 mmol, 4.0 eq.) was added. To this suspension benzyl bromide (14.6 g, 98.0 mmol, 2.5 eq.) was added and the reaction mixture was stirred at 20-25°C for 16 h. Excess of benzyl bromide was quenched with triethylamine (15 mL) at 40°C for 45 min. The reaction mixture was then cooled to 20-25 °C filtered and evaporated to dryness yielding a crude yellow oil. The crude product was purified by flash column chromatography (SiO_2, Methyl *tert*-butyl ether / pentane (3:7)) yielding a colourless oil (14.5 g, 25.3 mmol, 77.8%, mixture of diastereomers <10%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{35}H_{48}N_3O_4$ m/z=574.3639, found m/z= 574.3648.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 7.36-7.14 (m, 15H, H-15, H-16, H-17, H-20, H-21, H-22, H-26, H-27, H-28), 5.28 (bs, 1H, H-9), 5.07 (d, ^2J =12.3 Hz, 1H, H-24a), 5.02 (d, ^2J =12.3 Hz, 1H, H-24b), 3.68 (d, ^2J =14.0 Hz, 1H, H-18a), 3.65 (d, ^2J =13.8 Hz, 1H, H-13a), 3.64-3.58 (m, 1H, H-10), 3.60 (d, ^2J =14.0 Hz, 1H, H-18b),), 3.42 (d, ^2J =13.8 Hz, 1H, H-13b), 3.34 (q, ^3J =7.1 Hz, 1H, H-2), 2.80-2.74 (m, 1H, H-6), 2.75 (dd, ^2J = 12.8 Hz, ^3J =4.8 Hz, 1H, H-7a), 2.49 (dd, ^2J = 12.8 Hz, ^3J =8.7 Hz, 1H, H-7b), 2.40 (dd, ^2J =13.1 Hz, 5.4 Hz, 1H, H-11a), 2.33 (dd, ^2J =13.1 Hz, 9.0 Hz, 1H, H-11b), 1.46 (s, 9H, H-30), 1.12 (d, ^3J =7.1 Hz, 3H, H-4), 1.09 (d, ^3J =6.4 Hz, 3H, H-12), 0.96 (d, ^3J =6.4 Hz, 3H, H-8).

^{13}C-NMR (125.77 MHz, 298K, $CDCl_3$): δ=173.2 (C-3), 156.3 (C-23), 140.2 (C-14), 140.0 (C-19), 137.0 (C-25), 128.9 (C-20), 128.7 (C-15), 128.5 (C-arom.), 128.3 (C-arom.), 128.2 (C-arom.), 128.0 (C-26), 127.9 (C-arom.), 126.9 (C-arom.), 126.8 (C-arom.), 80.7 (C-29), 66.3 (C-24), 57.9 (C-2), 56.1 (C-18), 54.8 (C-13), 54.6 (C-11), 54.0 (C-7), 52.9 (C-6), 45.2 (C-10), 28.4 (C-30), 19.3 (C-12), 15.7 (C-4), 12.5. (C-8).

***N*-((*S*)-2-(((*S*)-2-Aminopropyl)(benzyl)amino)propyl)-*N*-benzyl-*L*-alanine (27)**



tert-Butyl (5S,8S,11S)-7,10-dibenzyl-5,8,11-trimethyl-3-oxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (**26**) (14.5 g, 25.3 mmol, 1.0 eq.) was dissolved in hydrobromic acid solution (16% wt. in acetic acid, 100 mL) and stirred at 40°C for 30 min. The solvent was removed under reduced pressure yielding a brownish oil. This oil was further suspended in acetonitrile (50 mL) and hydrochloric acid (37%, 5.0 mL). This mixture was again evaporated to dryness. The procedure was repeated three times to remove residual acetic acid from the product. Finally, the product was dissolved in methanol (50 mL) and evaporated to dryness, yielding a beige foam. This

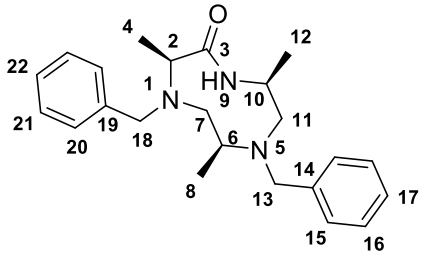
foam was extensively dried under high vacuum at 40°C for 2 days. The product (15.5 g) is obtained as a mixture of HCl and HBr salt with minimal acetate content and was further used without additional purification.

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{23}H_{34}N_3O_2$ m/z=384.2646, found m/z= 384.2648.

^{1}H-NMR (600.13 MHz, 298K, DMSO-d_6): δ= 7.80 (bs, 3H, H-9), 7.40-7.18 (m, 10H, H-15, H-16, H-17, H-20, H-21, H-22), 3.78 (d, ^2J =13.8 Hz, 1H, H-18a), 3.71 (d, ^2J =13.6 Hz, 1H, H-13a), 3.67 (d, ^2J =13.8 Hz, 1H, H-18b), 3.54 (d, ^2J =13.6 Hz, 1H, H-13b), 3.43 (q, ^3J =7.0 Hz, 1H, H-2), 3.21-3.12 (m, 1H, H-10), 3.00-2.85 (m, 2H, H-6, H-7a), 2.61 (dd, ^2J =17.6 Hz, ^3J =9.8 Hz, 1H, H-7b), 2.55-2.46 (m, 2H, H-11), 1.19 (d, ^3J =7.2 Hz, 3H, H-4), 1.08 (d, ^3J =7.4 Hz, 3H, H-12), 0.98 (d, ^3J =6.1 Hz, 3H, H-8).

^{13}C-NMR (100.77 MHz, 298K, DMSO-d_6): δ= 173.5 (C-3), 138.1 (C-19), 136.6 (C-14), 129.4 (C-20), 129.2 (C-15), 128.5 (C-21), 128.3 (C-16), 127.8 (C-22), 127.4 (C-17), 57.5 (C-2), 55.5 (C-18), 54.4 (C-13), 53.1 (C-11), 52.3 (C-7), 52.2 (C-6), 44.9 (C-10), 16.5 (C-12), 13.2 (C-4), 12.0 (C-8).

(3*S*,6*S*,9*S*)-4,7-Dibenzyl-3,6,9-trimethyl-1,4,7-triazonan-2-one (S35)



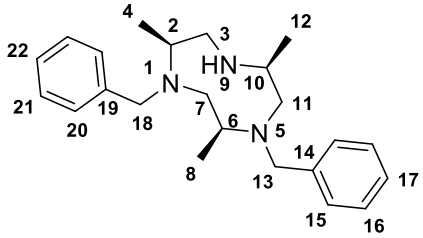
N-((*S*)-2-(((*S*)-2-Aminopropyl)(benzyl)amino)propyl)-*N*-benzyl-*L*-alanine **(28)** (3.00 g, 2.68 mmol, 1.0 eq.) and DIPEA (2.9 mL, 17.3 mmol, 5.0 eq.) were dissolved in acetonitrile (2.5 L). HATU (1.45 g, 3.81 mmol, 1.2´1 eq.) was added and the solution was stirred at 20-25°C for 30 min. The solvent was removed under vacuum. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate / cyclohexane (7:3)) yielding a white solid (800 mg, 2.19 mmol, 63.3% yield calculated over 2 steps).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{23}H_{32}N_3O$ m/z=366.2540, found m/z= 366.2535.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 8.24 (bs, 1H, H-9), 7.45-7.26 (m, 10H, H-15, H-16, H-17, H-20, H-21, H-22), 3.79 (d, ^2J =13.1 Hz, 1H, H-13a), 3.73 (d, ^2J =13.1 Hz, 1H, H-13b), 3.65 (d, ^2J =12.9 Hz, 1H, H-18a), 3.56 (d, ^2J =12.9 Hz, 1H, H-18b), 3.28 (q, ^3J =6.6 Hz, 1H, H-2), 2.93 (ddq, ^3J=11.8 Hz, ^3J =3.5 Hz, ^3J =6.5 Hz, 1H, H-6), 2.70 (ddq, ^3J =11.2 Hz, ^3J =2.8 Hz, ^3J =6.9 Hz, 1H, H-10), 2.62 (dd, ^2J =13.6 Hz, ^3J =11.2 Hz, 1H, H-11a), 2.32 (dd, ^2J =15.3 Hz, ^3J =11.8 Hz, 1H, H-7a), 2.20 (dd, ^2J =13.6 Hz, ^3J =2.8 Hz, 1H, H-11b), 2.17 (dd, ^2J =15.3 Hz, ^3J =3.5 Hz, 1H, H-7b), 1.42 (d, ^3J =6.9 Hz, 3H, H-12), 1.04 (d, ^3J =6.6 Hz, 3H, H-4), 0.79 (d, ^3J =6.5 Hz, 3H, H-8).

^{13}C-NMR (125.77 MHz, 298K, $CDCl_3$): δ= 180.9 (C-3), 140.4 (C-14), 139.0 (C-19), 129.2 (C-15), 129.1 (C-20), 128.6 (C-16), 128.6 (C-21), 127.5 (C-17), 127.4 (C-22), 60.2 (C-13), 59.1 (C-2), 57.2 (C-18), 55.7 (C-7), 54.5 (C-6), 53.8 (C-11), 51.9 (C-10), 16.3 (C-12), 10.4 (C-8), 6.6 (C-4).

(2*S*,5*S*,8*S*)-1,4-Dibenzyl-2,5,8-trimethyl-1,4,7-triazonane (29)



(3*S*,6*S*,9*S*)-4,7-Dibenzyl-3,6,9-trimethyl-1,4,7-triazonan-2-one **(28)** (779 mg, 2.13 mmol, 1.0 eq.) was dissolved in dichloromethane (5 mL) and cooled to 0-5 °C. Trimethylsilyl chloride (1.15 g, 10.7 mmol, 5.0 eq.) was slowly added and the reaction mixture was

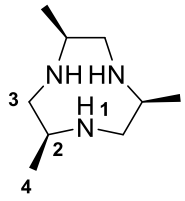
stirred at 0-5 °C for 30 min followed by the addition of lithium aluminium hydride (8.9 mL, 2 M in THF, 21.3 mmol, 10.0 eq.). The reaction mixture was allowed to warm to 20-25 °C and was further stirred for 5 h. The reaction mixture was cooled to 0-5 °C and saturated aqueous sodium hydrogen carbonate (2 mL) was slowly added. To the resulting suspension sodium sulphate (3 g) was added. The suspension was filtered and evaporated to dryness yielding a white solid (730 mg, 4.04 mmol, 97.5%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_{23}H_{34}N_3$ m/z=352.2747, found m/z= 352.2747.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ=7.37-7.08 (m, 10H, H-15, H-16, H-17, H-20, H-21, H-22), 3.61 (d, ^2J =13.0 Hz, 1H, H-18a), 3.56 (d, ^2J =13.0 Hz, 1H, H-18b), 3.53 (d, ^2J =12.7 Hz, 1H, H-13a), 3.52 (d, ^2J =12.7 Hz, 1H, H-13b), 3.15-3.04 (m, 1H, H-2), 3.03-2.93 (m, 1H, H-3a), 2.85-2.75 (m, 1H, H-10), 2.59-2.48 (m, 1H, H-6), 2.41 (dd, ^2J =15.2 Hz, ^3J =12.1 Hz, 1H, H-11a), 2.28 (dd, ^2J =15.4 Hz, ^3J =12.1 Hz, 1H, H-7a), 2.20 (dd, ^3J =12.6 Hz, ^3J =12.3 Hz, 1H, H-3b), 2.17 (dd, ^2J =15.2 Hz, ^3J =4.2 Hz, 1H, H-11b), 2.07 (dd, ^2J =15.4 Hz, ^3J =4.3 Hz, 1H, H-7b), 1.04 (d, ^3J =6.7 Hz, 3H, H-12), 0.86 (d, ^3J =6.4 Hz, 3H, H-4), 0.71 (d, ^3J =6.4 Hz, 3H, H-8).

^{13}C-NMR (125.77 MHz, 298K, $CDCl_3$): δ= 138.3 (C-14), 137.9 (C-19), 129.2 (C-arom.), 129.2 (C-arom.), 129.1 (C-arom.), 128.9 (C-arom.), 128.2 (C-arom.), 128.0 (C-arom.), 59.5 (C-13), 58.7 (C-18), 53.6 (C-6), 52.1 (C-2), 51.6 (C-10), 50.3 (C-7), 47.2 (C-11), 41.5 (C-3), 12.9 (C-12), 11.0 (C-4), 11.0 (C-8).

(2*S*,5*S*,8*S*)-2,5,8-Trimethyl-1,4,7-triazonane (M3-TACN)



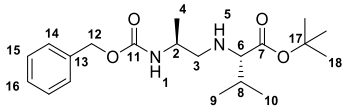
(2*S*,5*S*,8*S*)-1,4-Dibenzyl-2,5,8-trimethyl-1,4,7-triazonane (**29**) (1.60 g, 4.45 mmol, 1.0 eq.), palladium hydroxide on carbon (300 mg, 20 wt. % loading) and ammonium formate (5.74 g, 91.0 mmol, 20.0 eq.) were suspended in ethanol (50 mL) and heated to reflux. The suspension was refluxed for 5 h, cooled to 20-25 °C, filtered over celite and evaporated to dryness. The residue was dissolved in dichloromethane (20 mL) and aqueous sodium hydroxide (2M, 20 mL). The layers were separated, and the organic layer was dried over sodium sulphate and evaporated to dryness yielding a colourless oil (510 mg, 2.98 mmol, 65.4%).

HR-ESI-MS: calcd. for $[M+H]^+$ $C_9H_{22}N_3$ m/z=172.1808, found m/z= 172.1811.

^{1}H-NMR (500.13 MHz, 298K, $CDCl_3$): δ= 2.77-2.69 (m, 3H, H-2), 2.66 (dd, ^2J =13.4 Hz, ^3J =4.2 Hz, 3H, H-3a), 2.37 (dd, ^2J =13.4 Hz, ^3J =9.0 Hz, 3H, H-3a), 1.95 (bs, 3H, H-1) 1.00 (d, ^3J =6.5 Hz, 9H, H-4).

^{13}C-NMR (100.62 MHz, 298K, $CDCl_3$): δ= 50.9 (C-2), 49.2 (C-3), 20.7 (C-4).

$[\alpha_D^{20}]$ + 147.2° (c 1.00, $CHCl_3$).


4
5
14
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O
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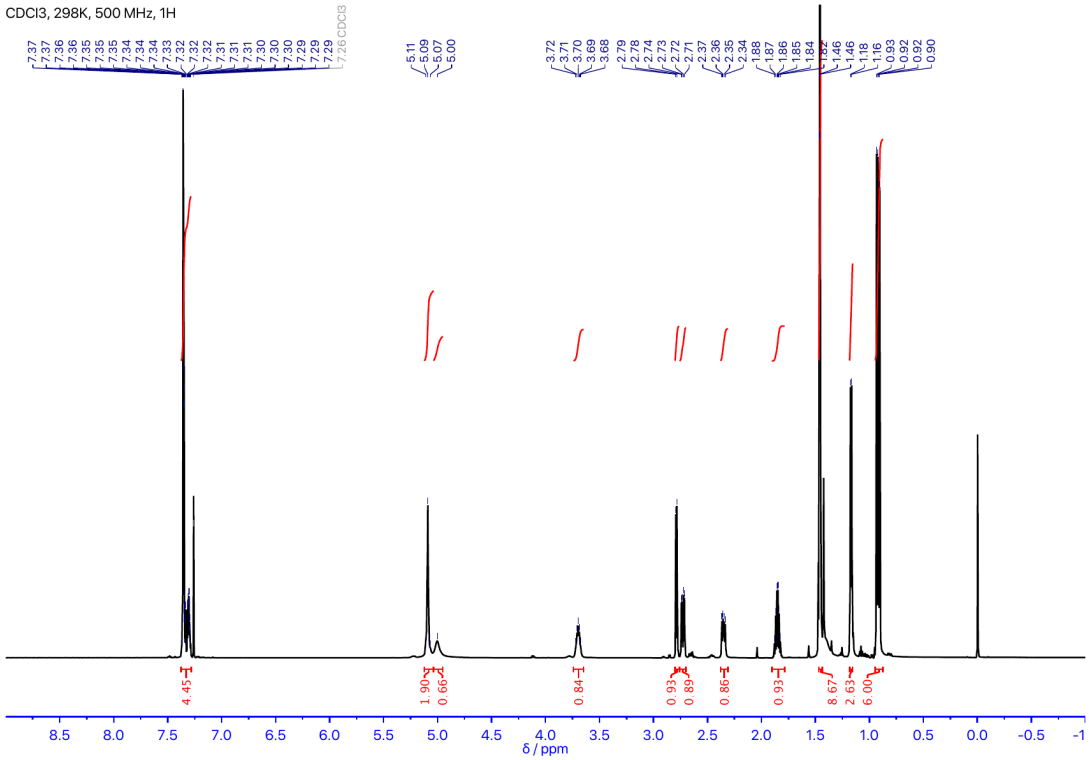
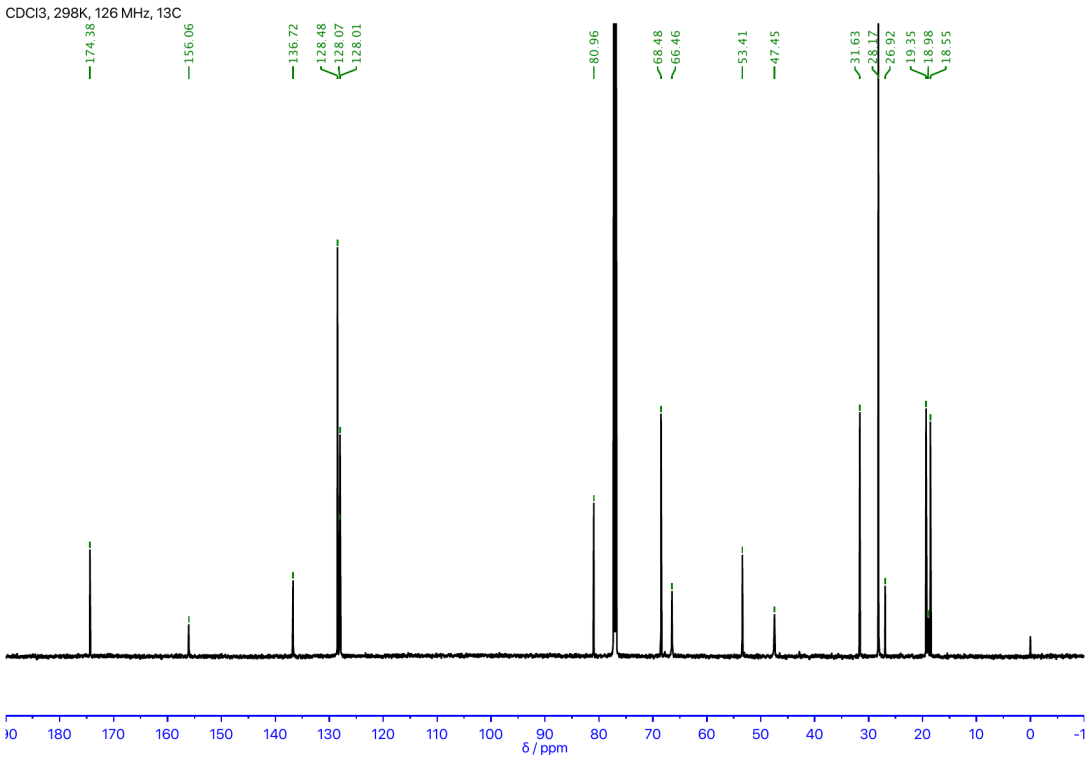
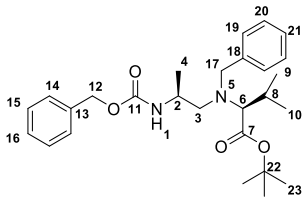
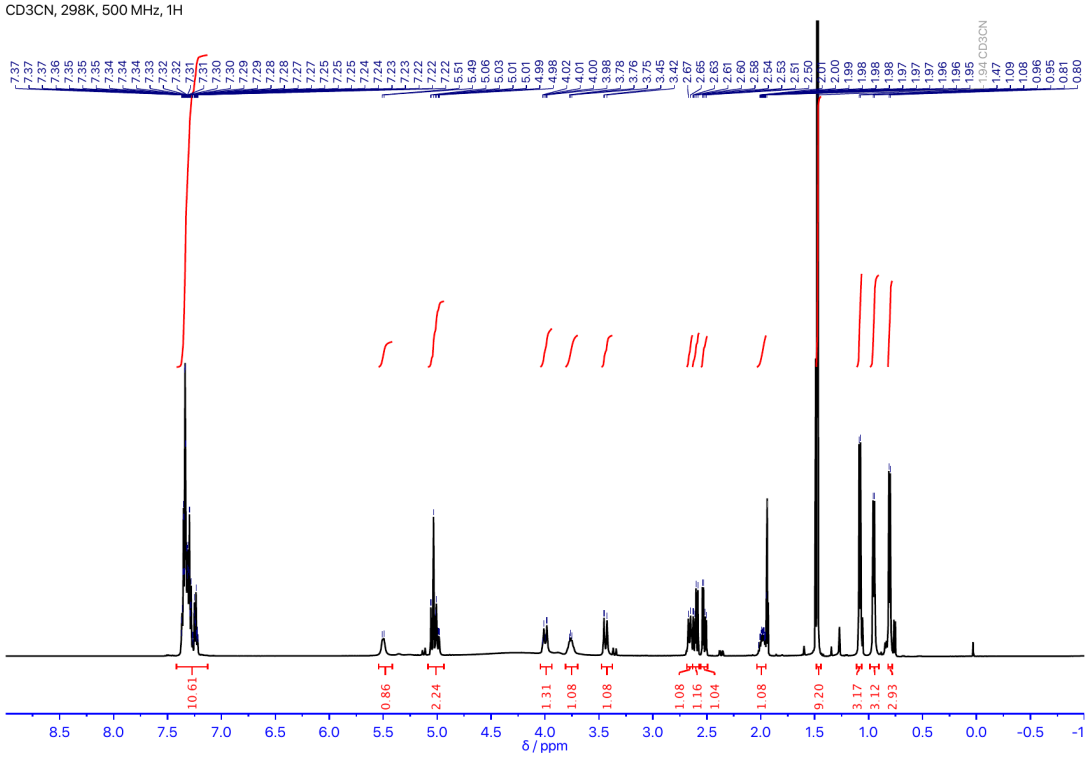
8
10


CDCl3, 298K, 500 MHz, 1H
7.37
7.37
7.36
7.36
7.35
7.35
7.35
7.34
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.30
7.29
7.29
7.29
7.26 CDCl3
5.11
5.09
5.07
5.00
3.72
3.71
3.70
3.69
3.68
2.79
2.78
2.74
2.73
2.72
2.71
2.37
2.36
2.35
2.34
1.88
1.87
1.86
1.85
1.84
1.82
1.46
1.46
1.18
1.16
0.93
0.92
0.92
0.90
4.45
1.90
0.66
0.84
0.93
0.89
0.86
0.93
8.67
2.63
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
δ / ppm

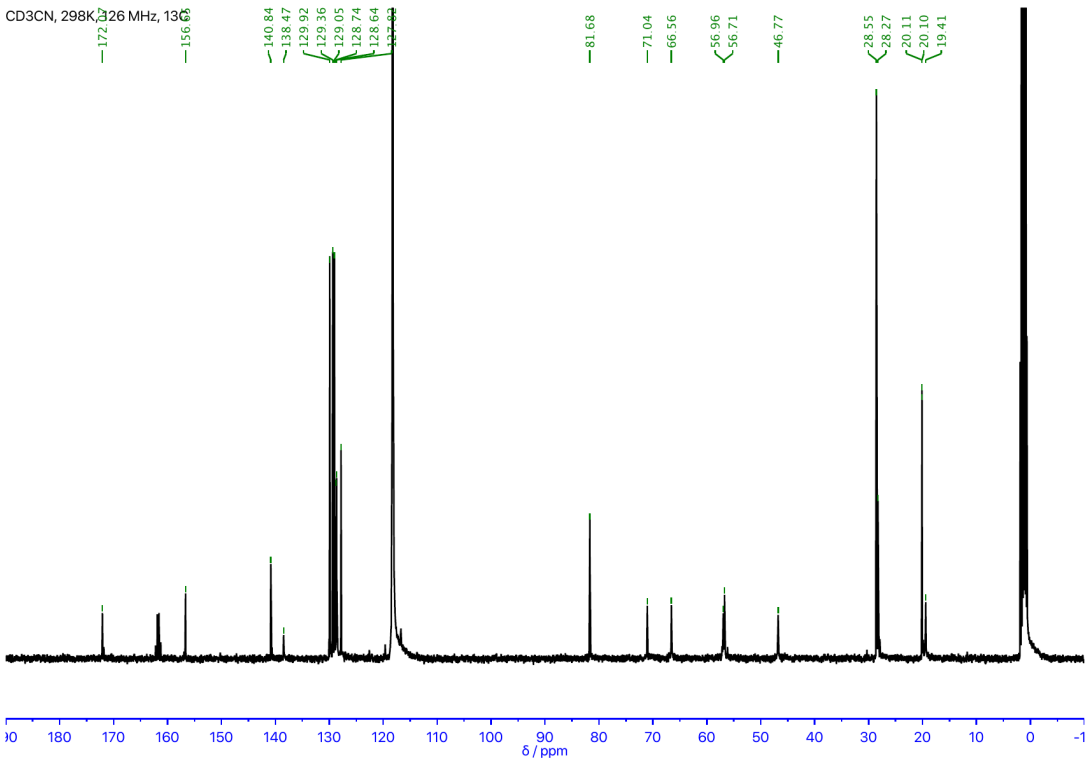

CDCl3, 298K, 126 MHz, 13C
174.38
156.06
136.72
128.48
128.07
128.01
80.96
68.48
66.46
53.41
47.45
31.63
28.17
26.92
19.35
18.98
18.55
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
δ / ppm

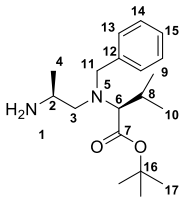


CD3CN, 298K, 500 MHz, 1H

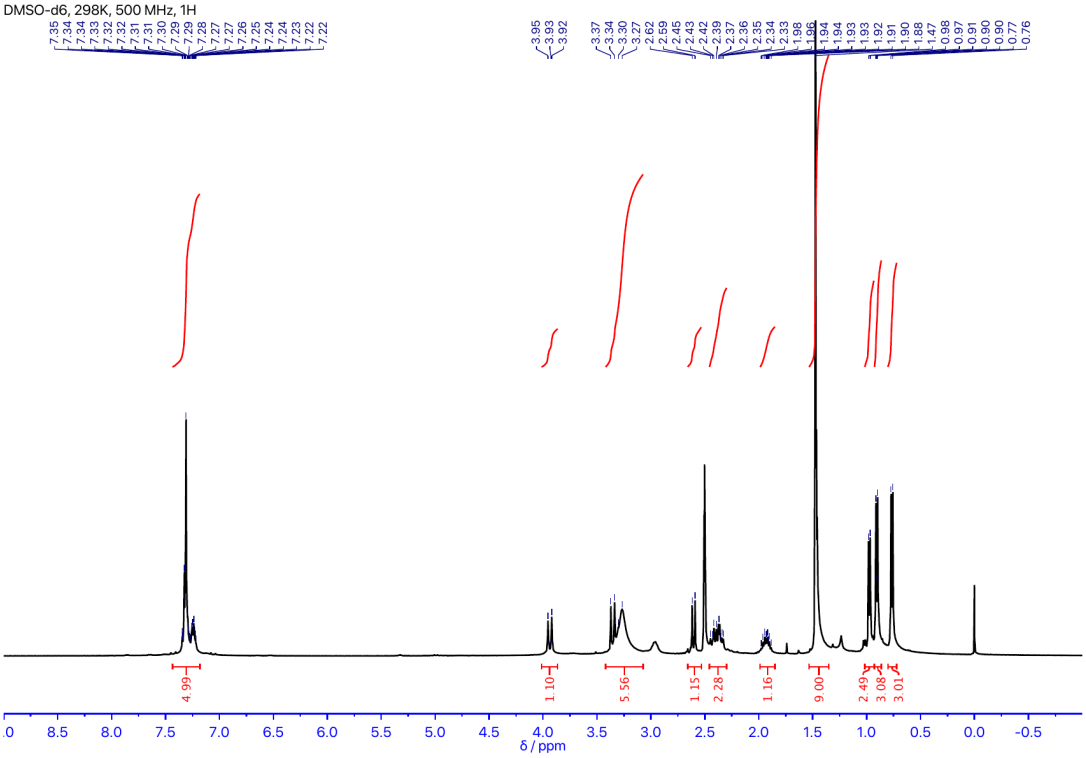


CD3CN, 298K, 126 MHz, 13C

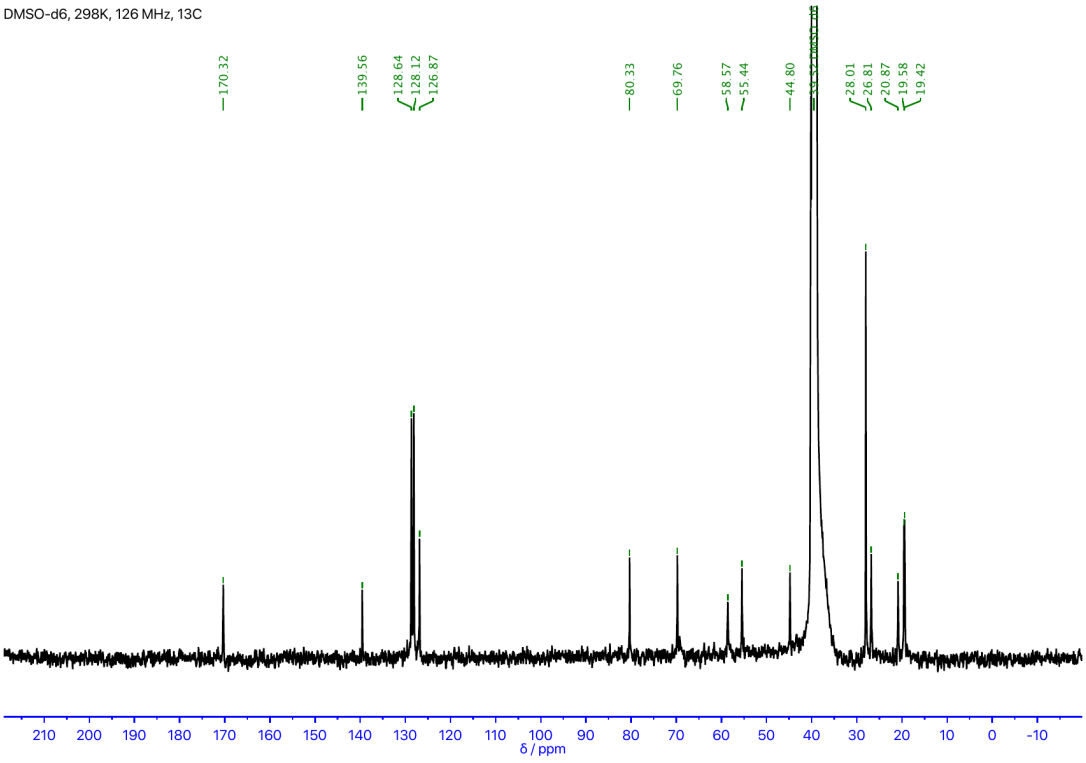


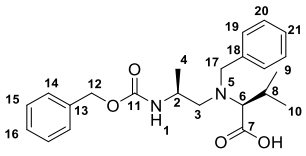


DMSO-d6, 298K, 500 MHz, 1H

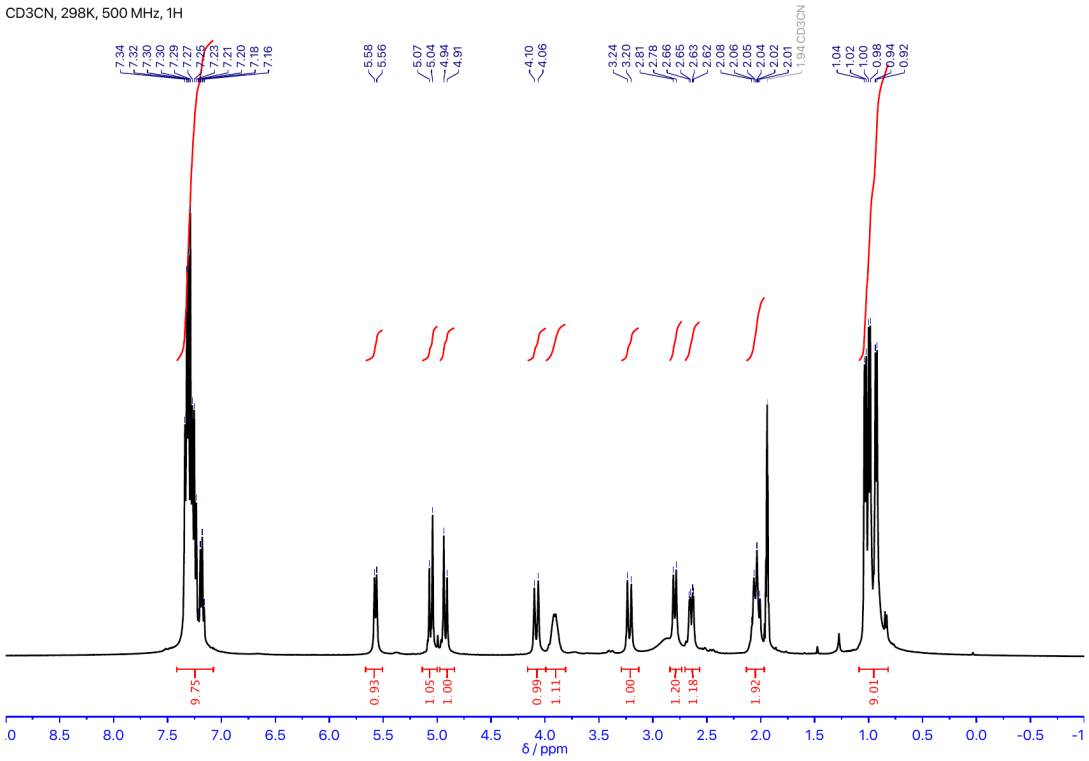


DMSO-d6, 298K, 126 MHz, 13C

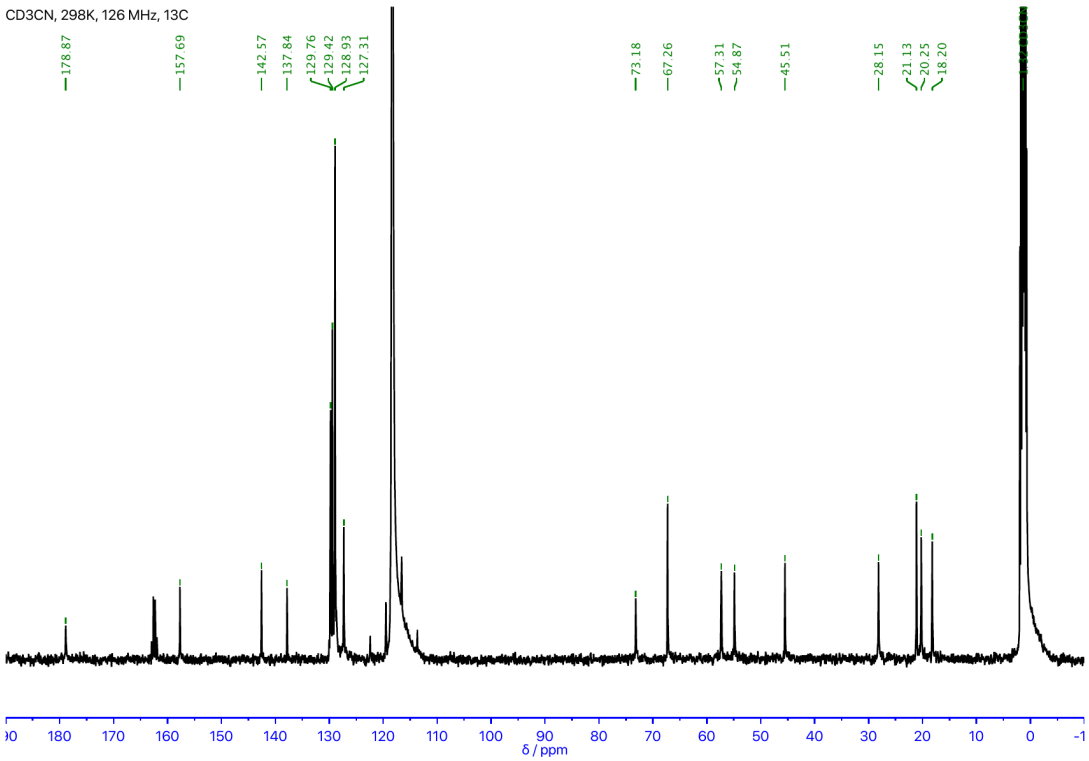


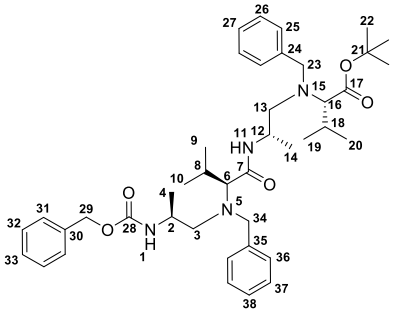


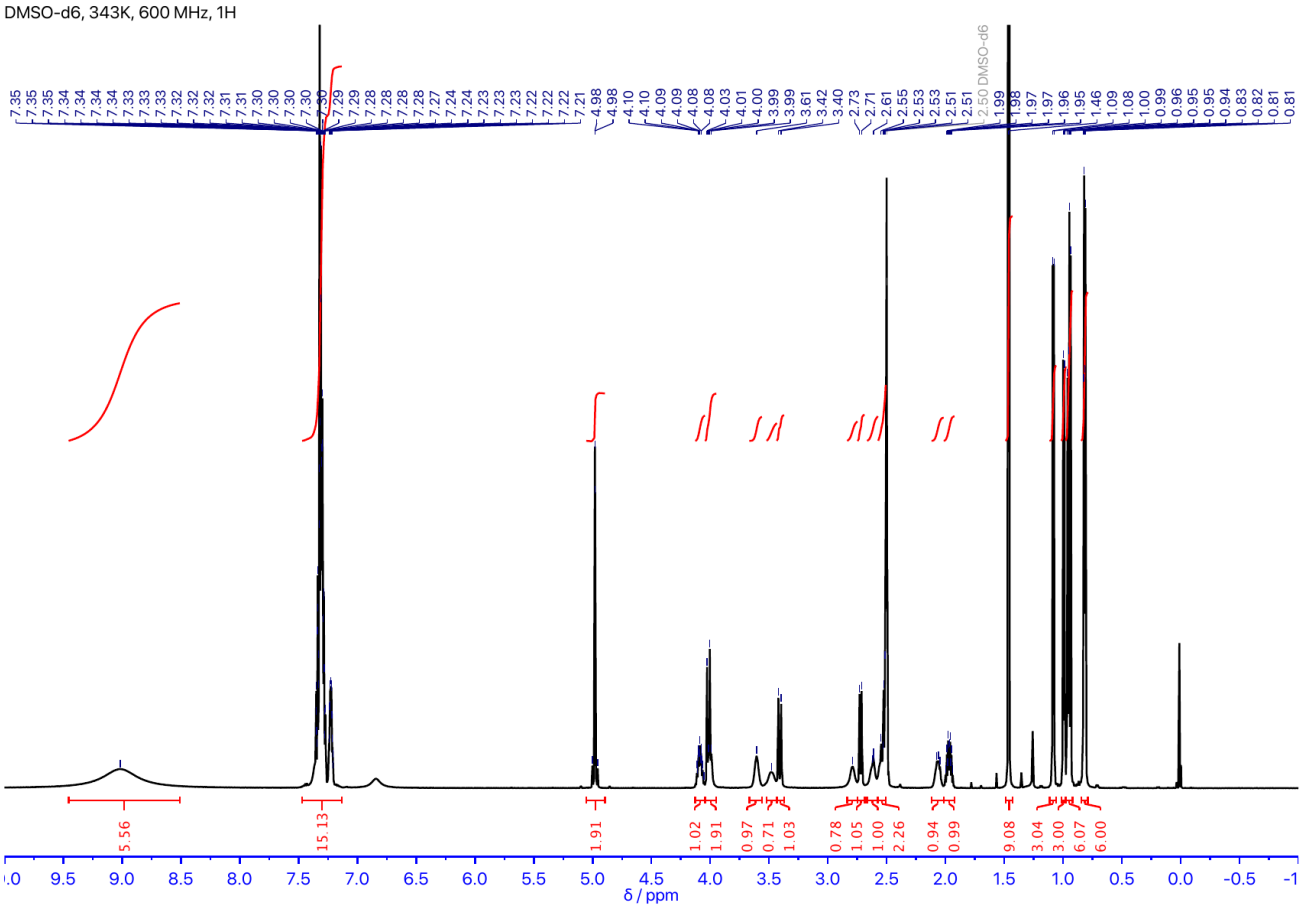
CD3CN, 298K, 500 MHz, 1H

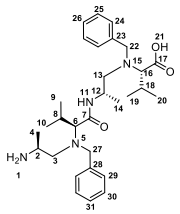


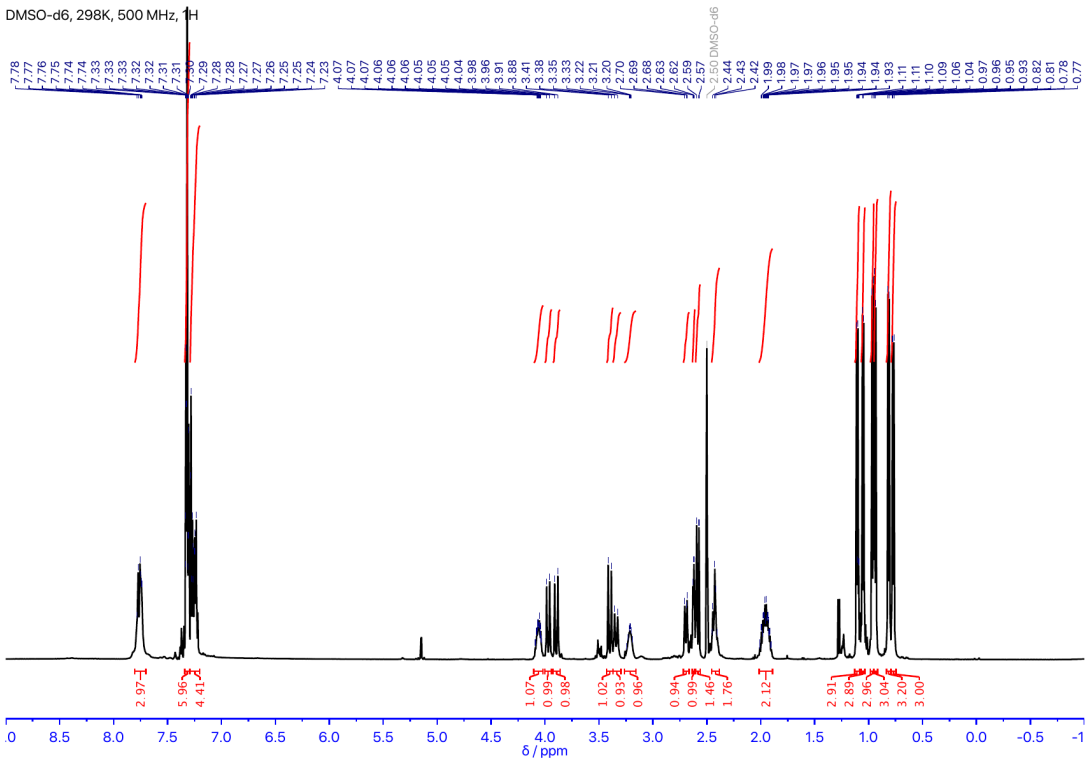
CD3CN, 298K, 126 MHz, 13C

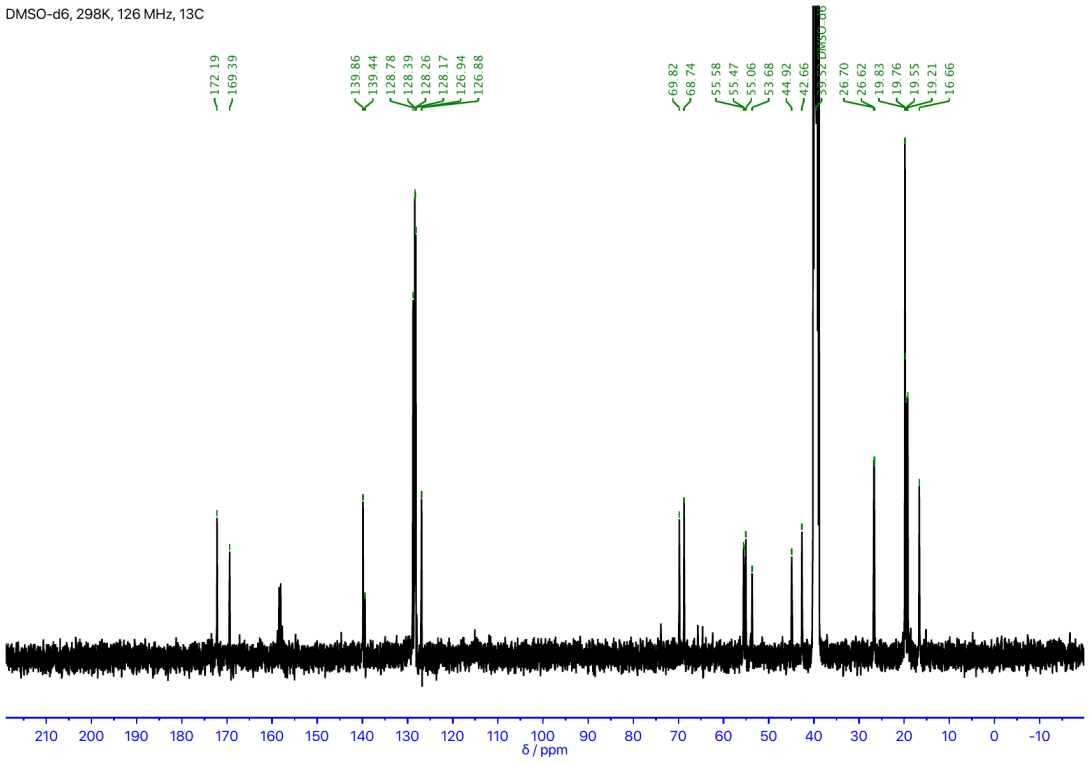


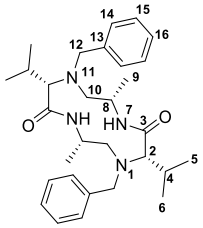


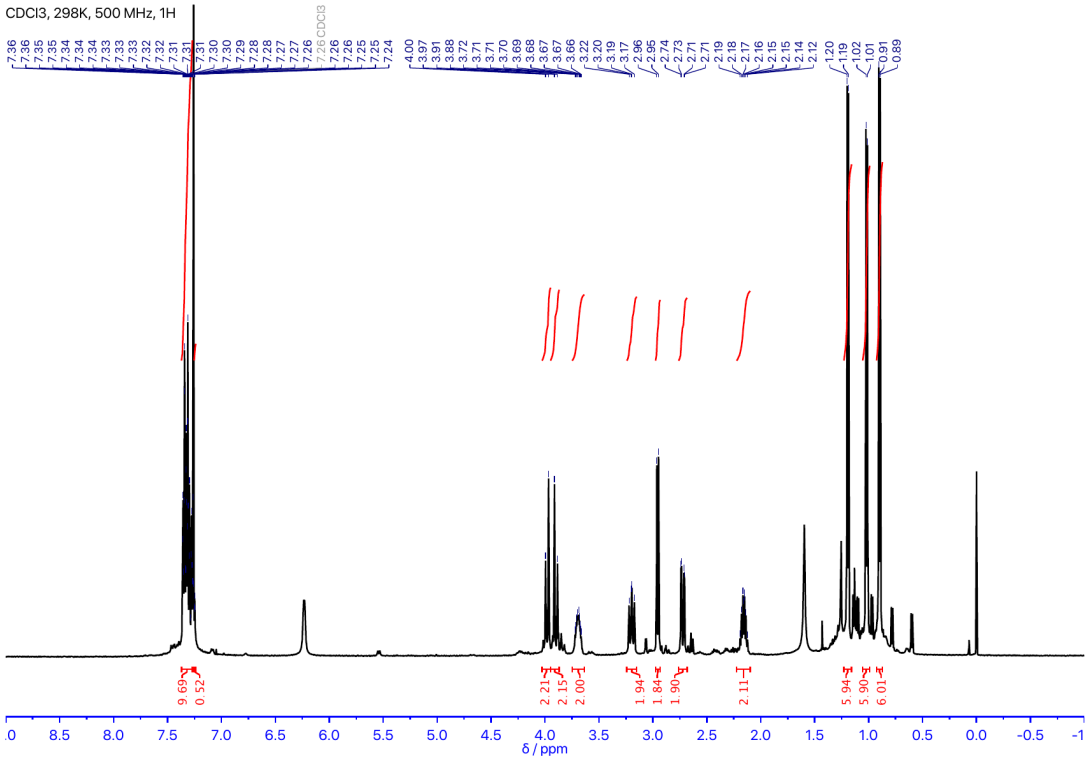

DMSO-d6, 343K, 600 MHz, 1H
δ / ppm

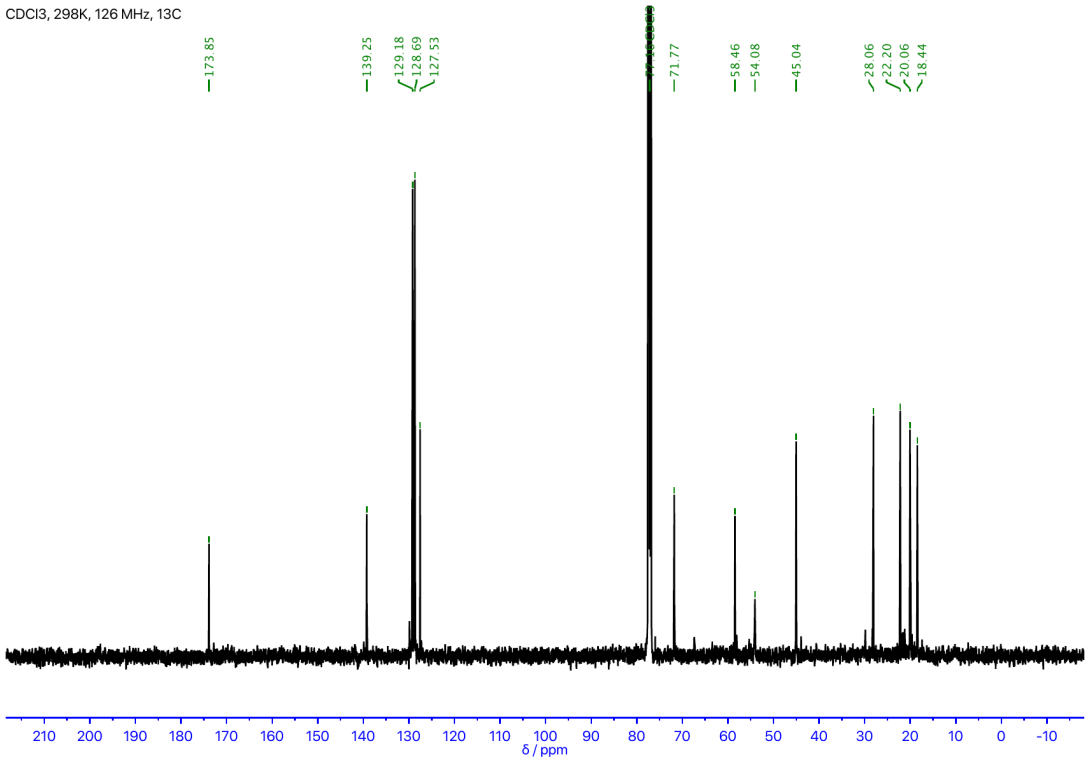


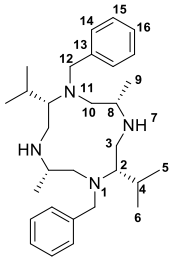

DMSO-d6, 298K, 500 MHz, 1H
δ / ppm

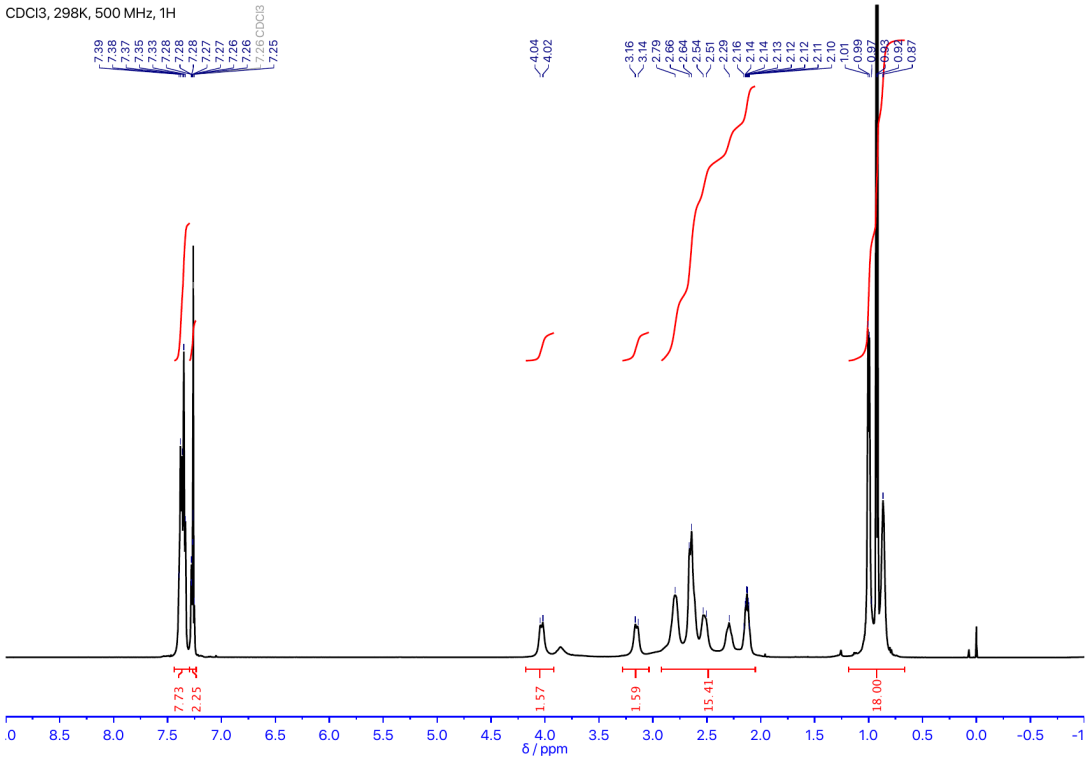

DMSO-d6, 298K, 126 MHz, 13C
δ / ppm

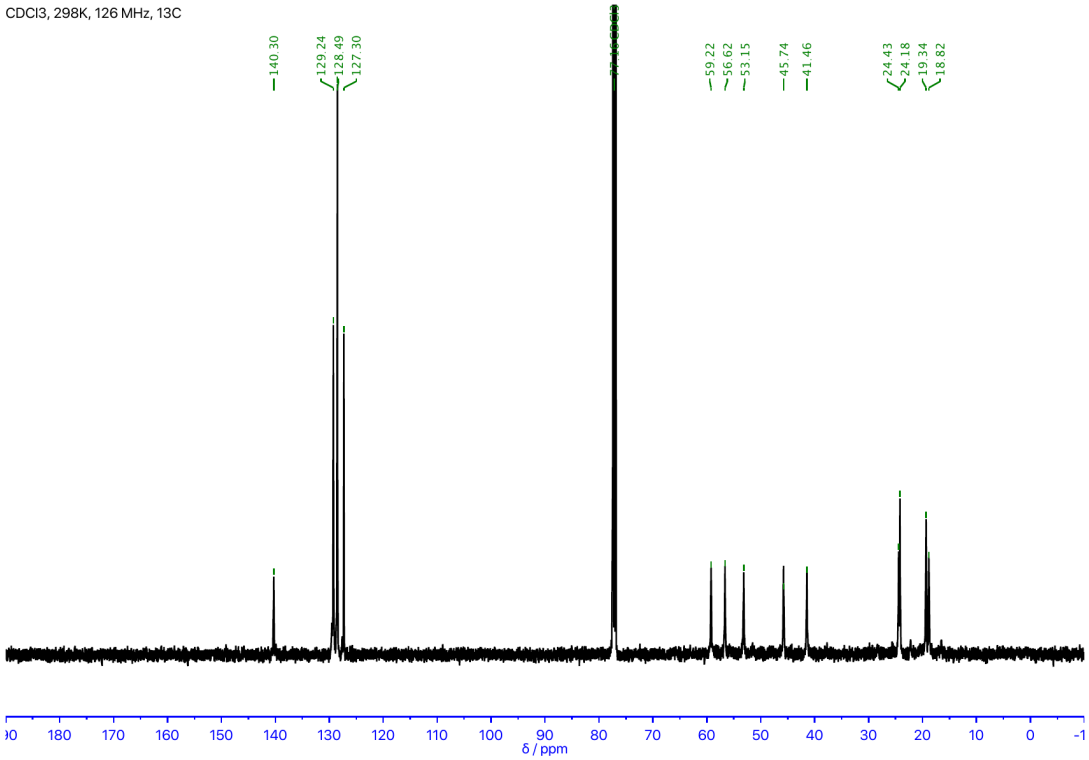

14
15
12
13
16
N
11
10
9
8
7
3
O
NH
HN
O
2
5
N
1
4
6

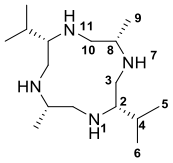

CDCl3, 298K, 500 MHz, 1H
δ / ppm


CDCl3, 298K, 126 MHz, 13C
173.85
139.25
129.18
128.69
127.53
71.77
58.46
54.08
45.04
28.06
22.20
20.06
18.44
δ / ppm

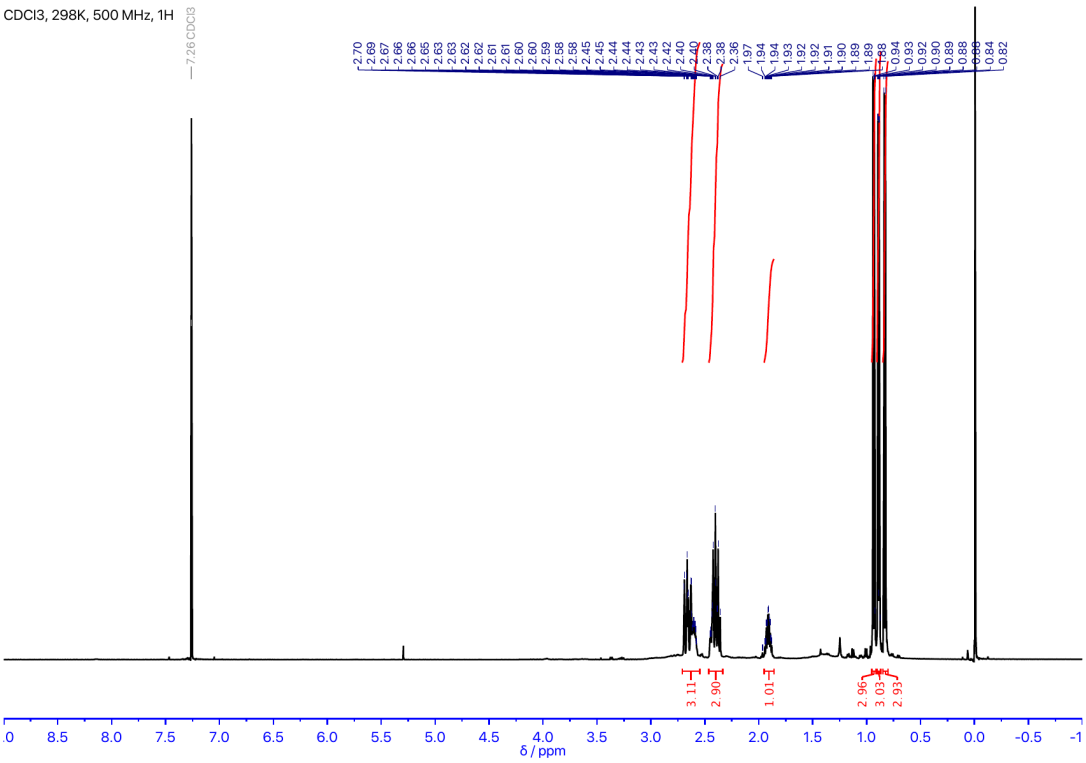

15
14
16
13
12
N
11
9
10
8
NH
7
HN
3
2
5
N
1
4
6


CDCl3, 298K, 500 MHz, 1H
7.39
7.38
7.37
7.35
7.33
7.28
7.28
7.28
7.27
7.27
7.26
7.26 CDCl3
7.25
4.04
4.02
3.16
3.14
2.79
2.66
2.64
2.54
2.51
2.29
2.16
2.14
2.13
2.12
2.12
2.11
2.10
1.01
0.99
0.97
0.93
0.92
0.87
7.73
2.25
1.57
1.59
15.41
18.00
δ / ppm

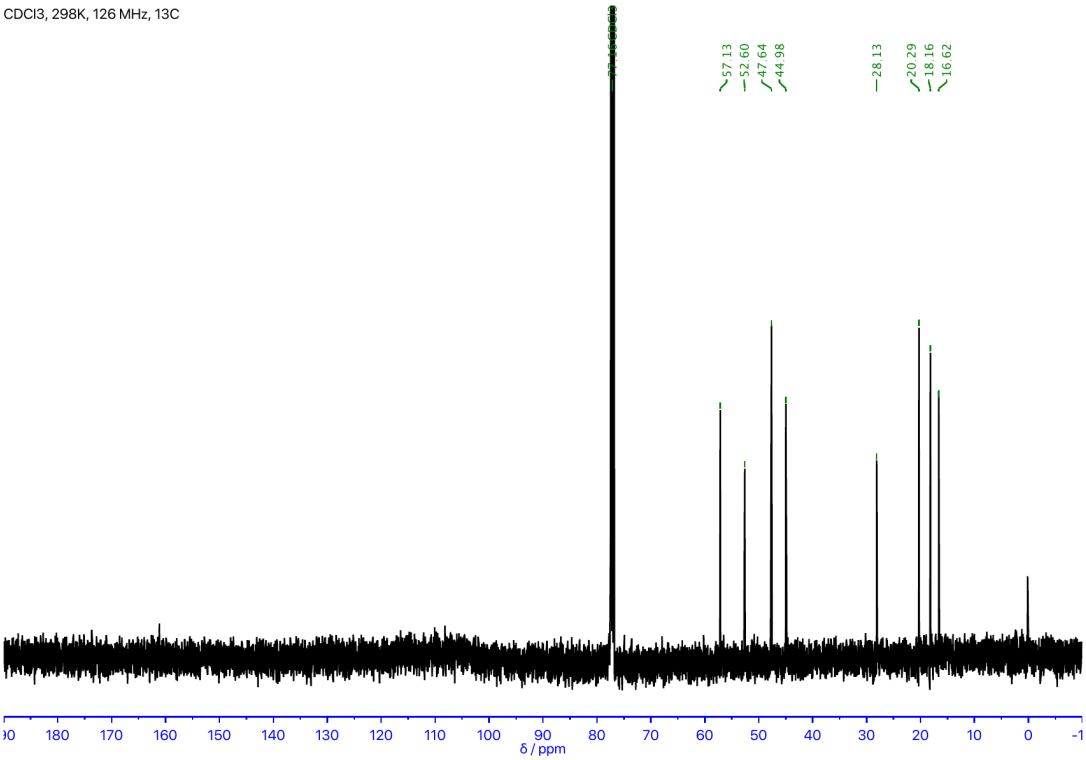

CDCl3, 298K, 126 MHz, 13C
140.30
129.24
128.49
127.30
77.16 CDCl3
59.22
56.62
53.15
45.74
41.46
24.43
24.18
19.34
18.82
δ / ppm

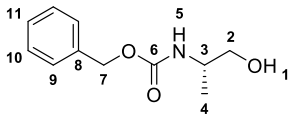


CDCl3, 298K, 500 MHz, 1H

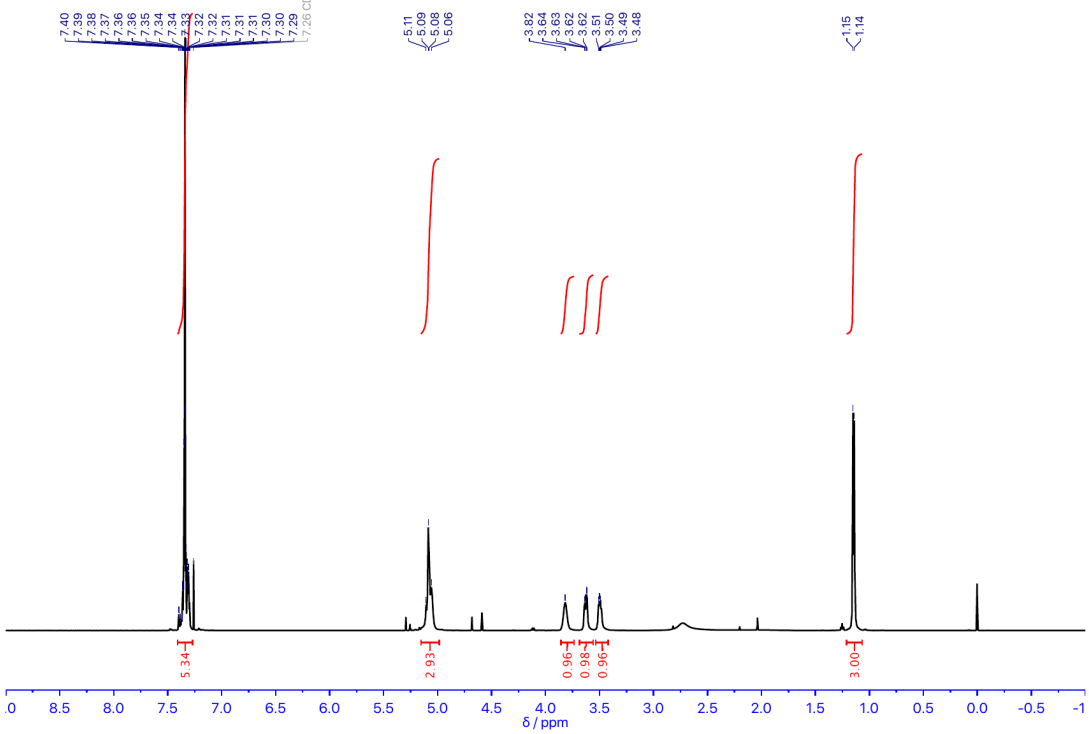


CDCl3, 298K, 126 MHz, 13C

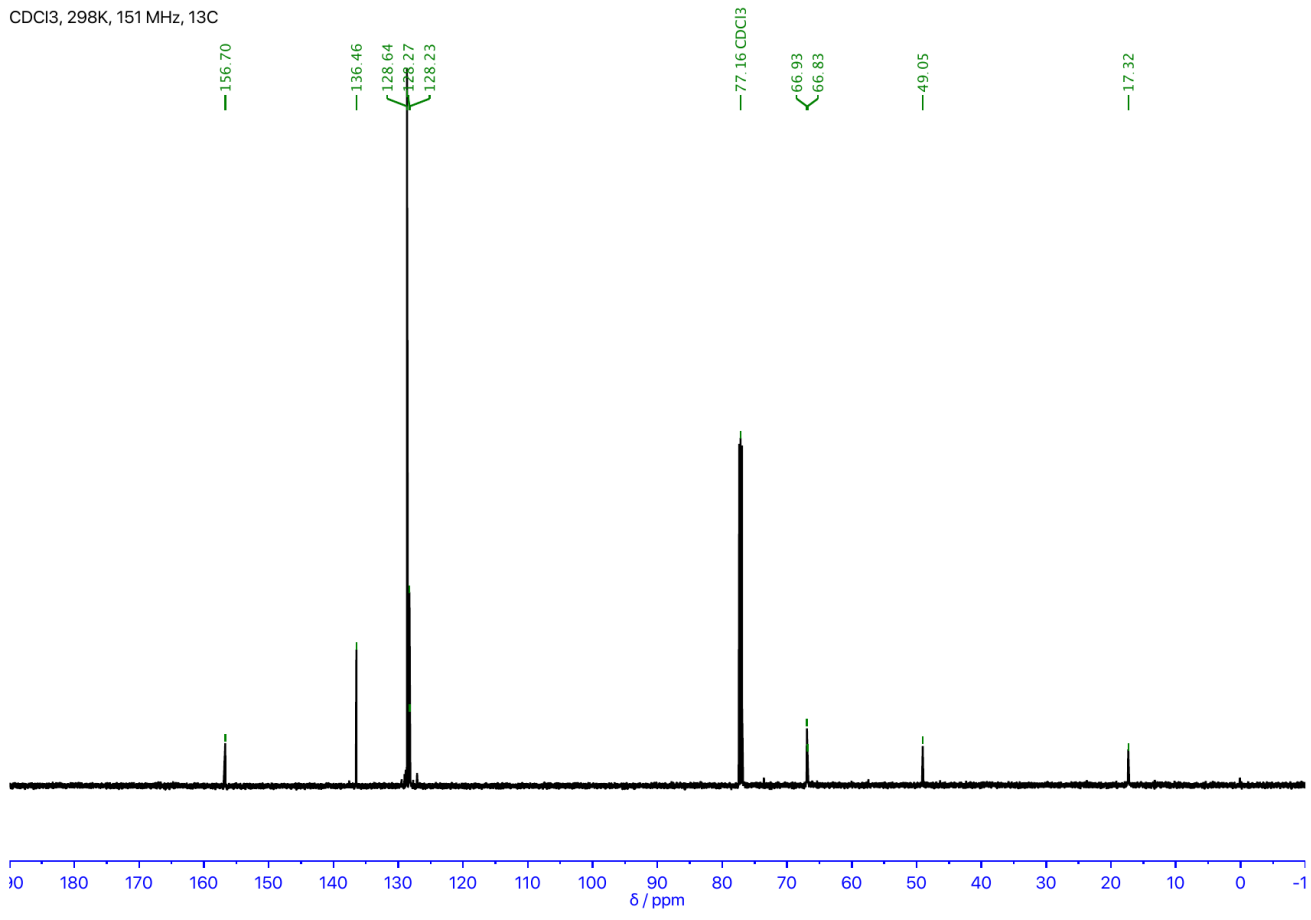


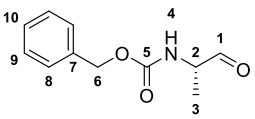


CDCl3, 298K, 600 MHz, 1H

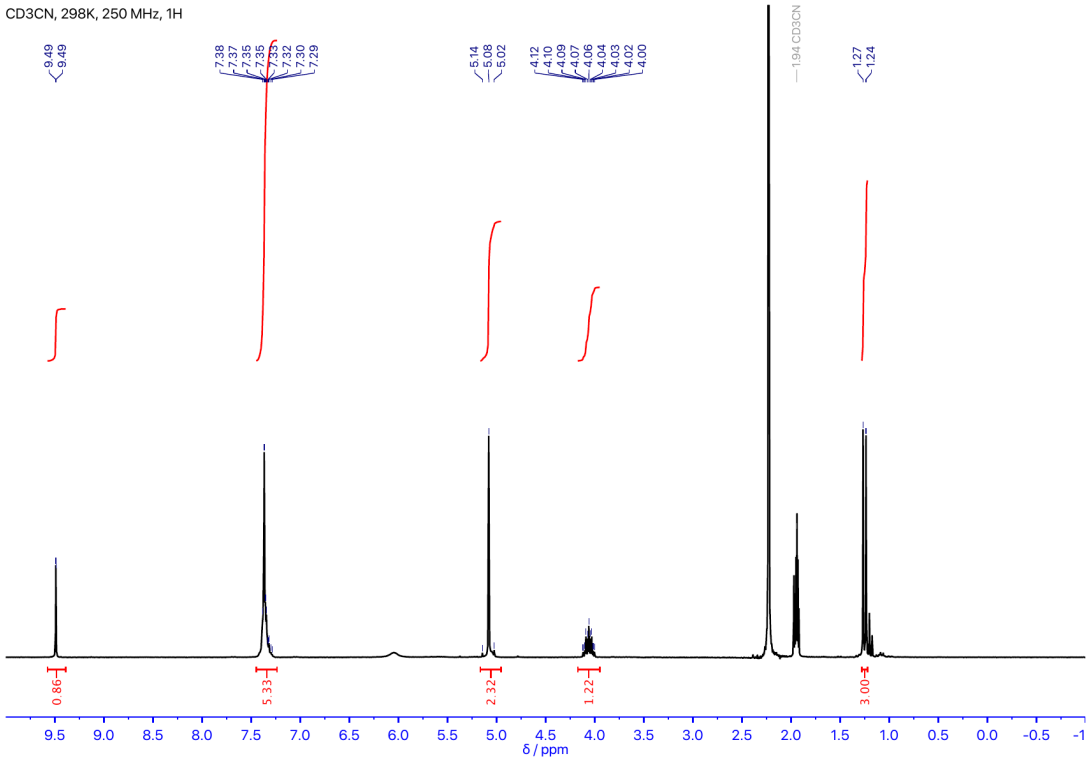


CDCl3, 298K, 151 MHz, 13C

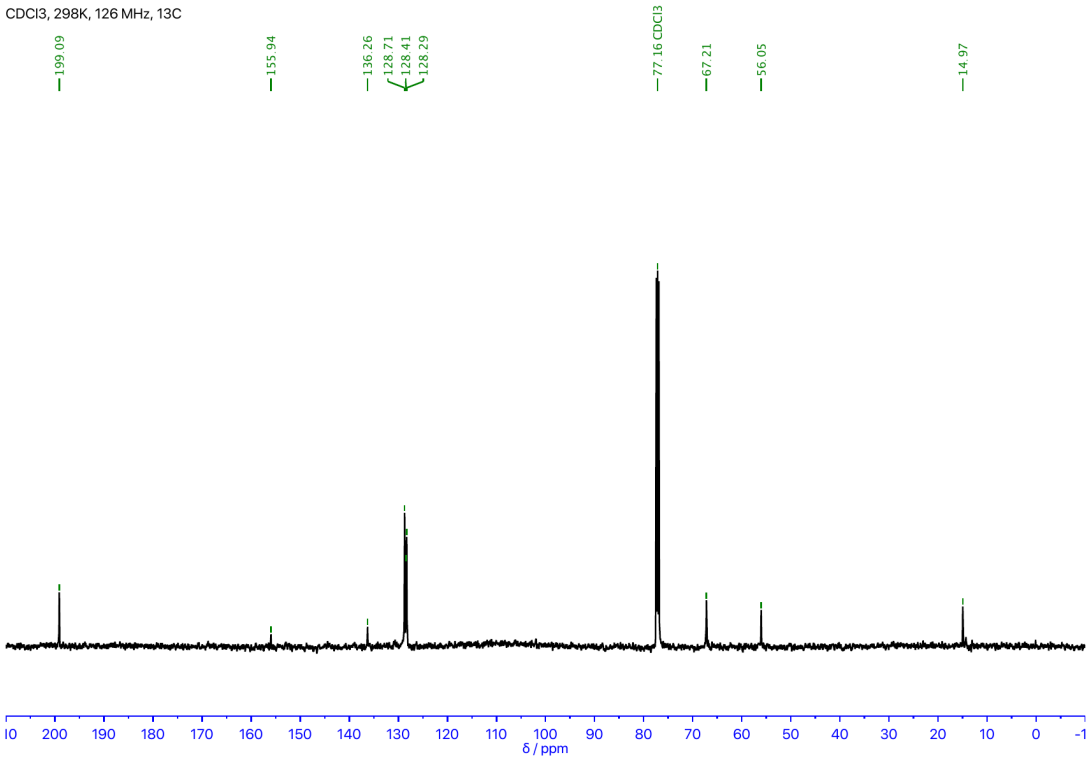


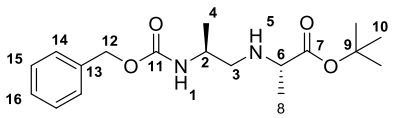


CD3CN, 298K, 250 MHz, 1H

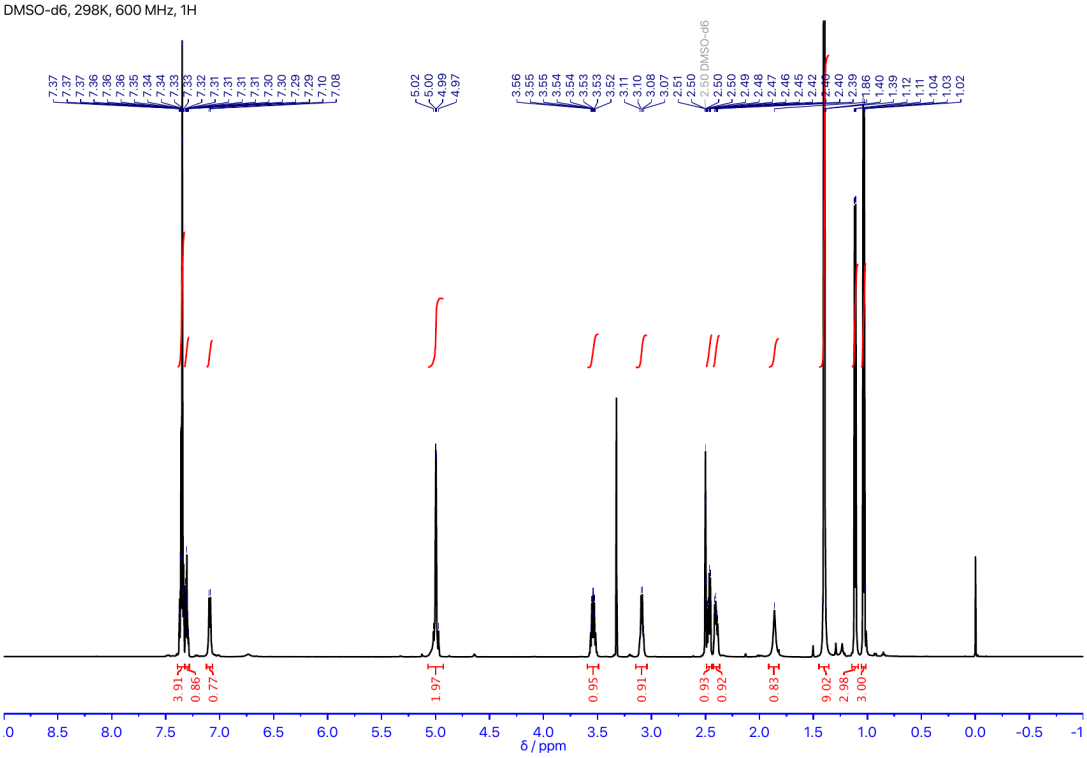


CDCl3, 298K, 126 MHz, 13C

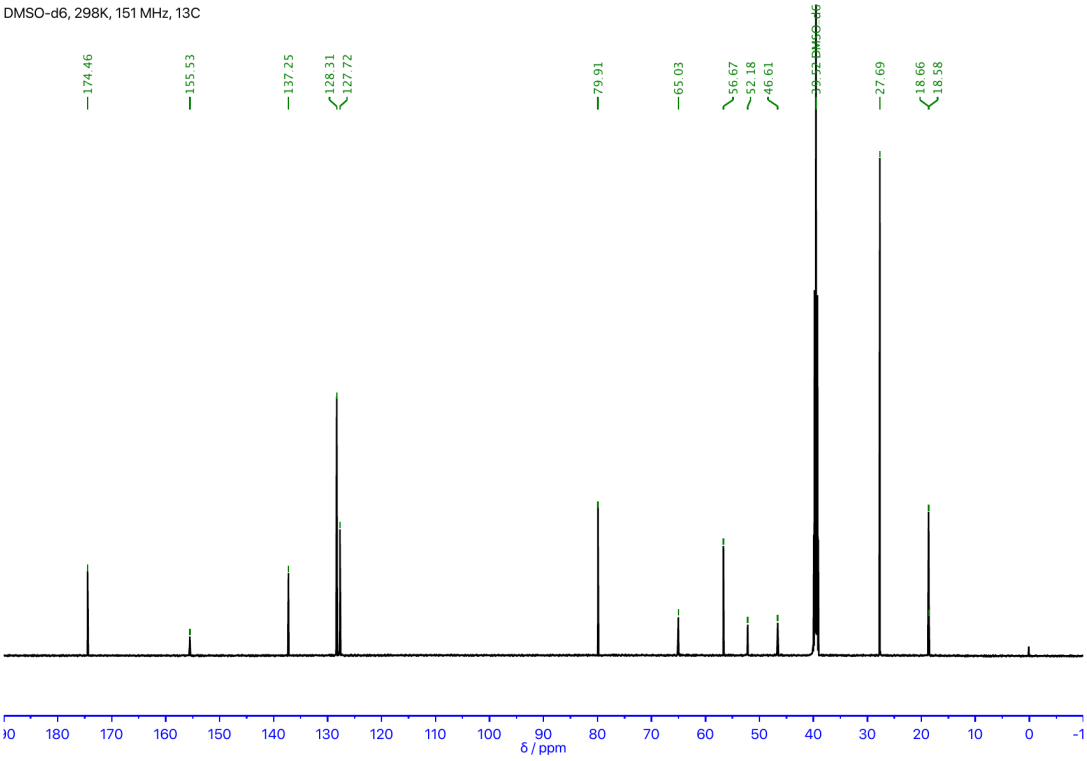


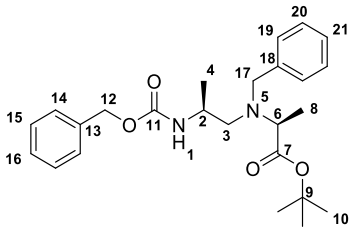


DMSO-d6, 298K, 600 MHz, 1H

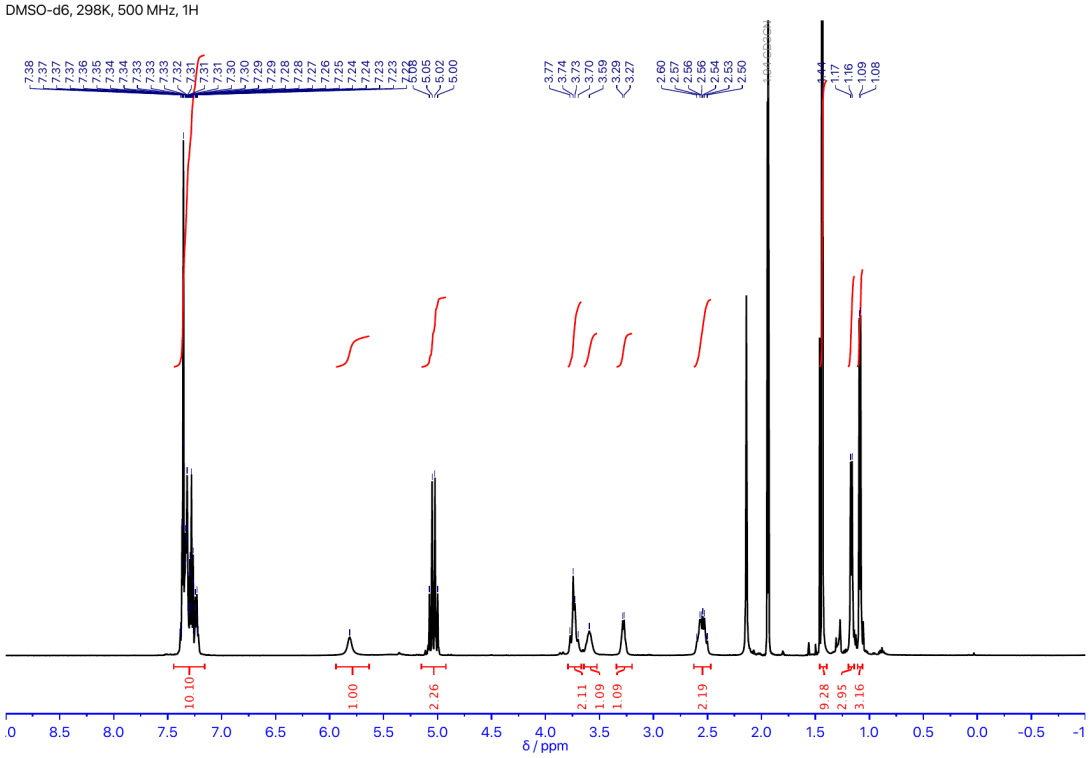


DMSO-d6, 298K, 151 MHz, 13C

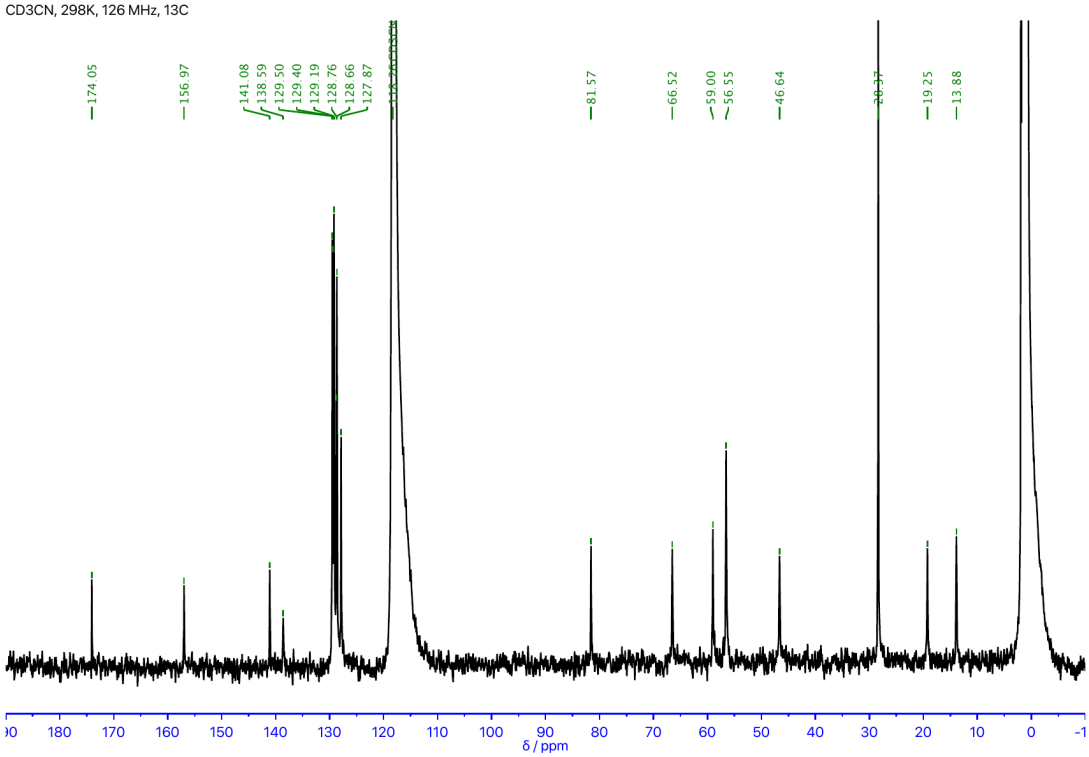


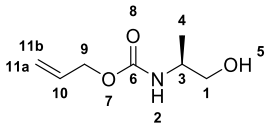


DMSO-d6, 298K, 500 MHz, 1H

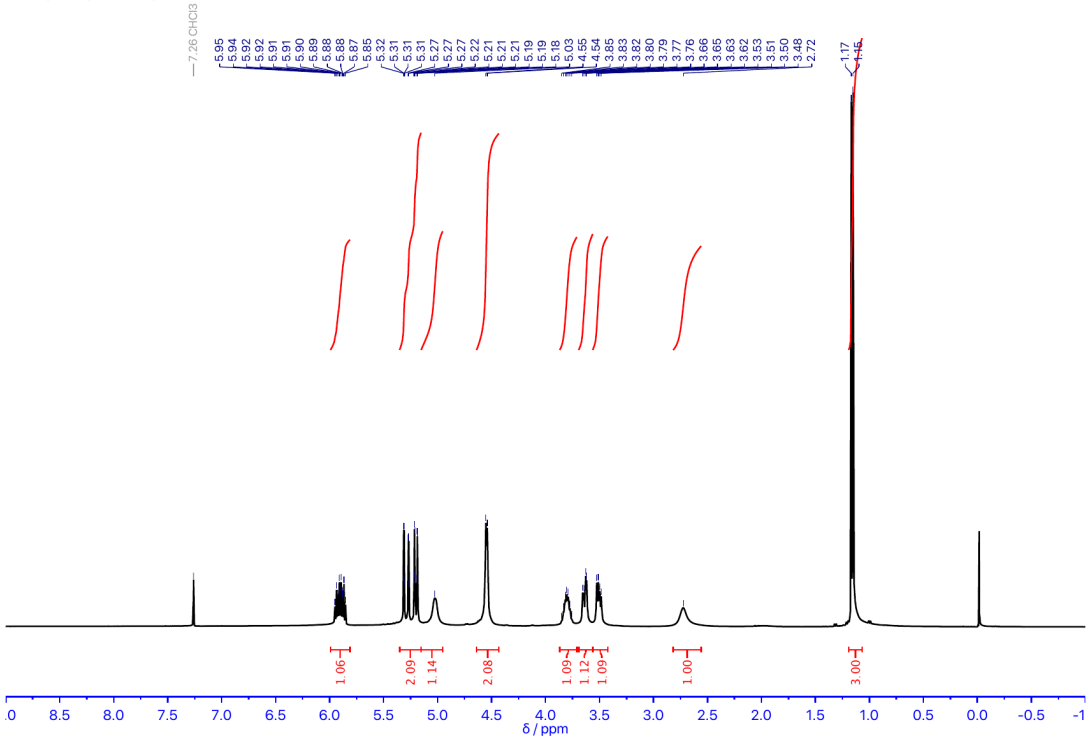


CD3CN, 298K, 126 MHz, 13C

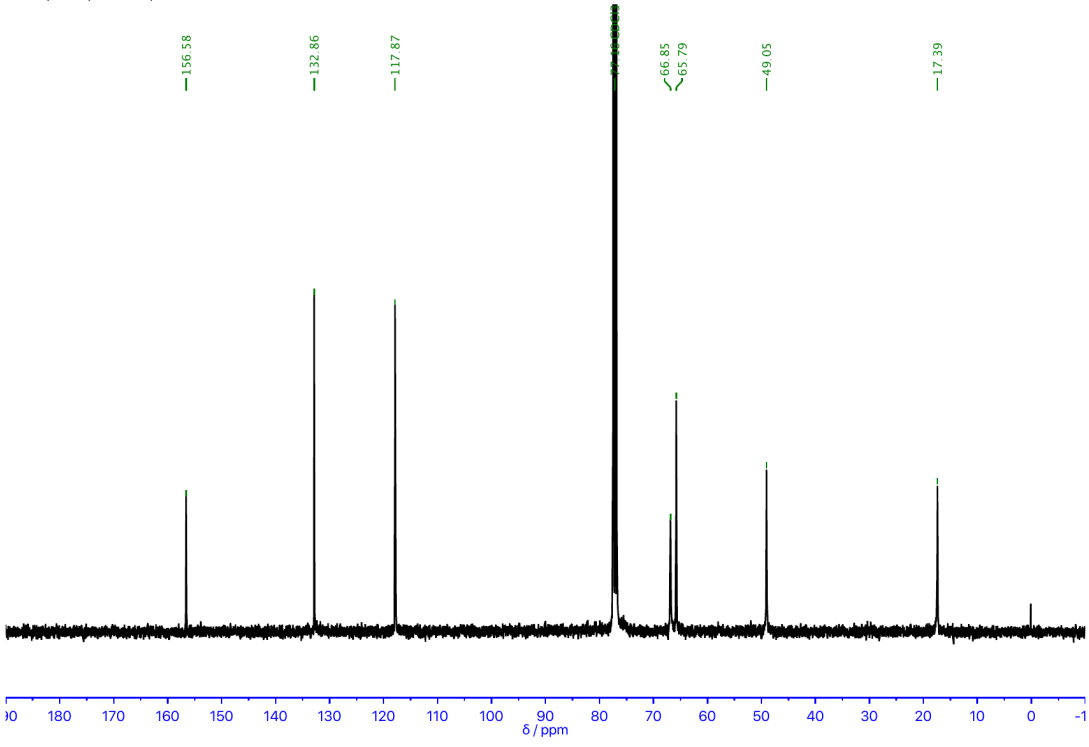


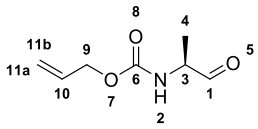


CDCl3, 298K, 500 MHz, 1H

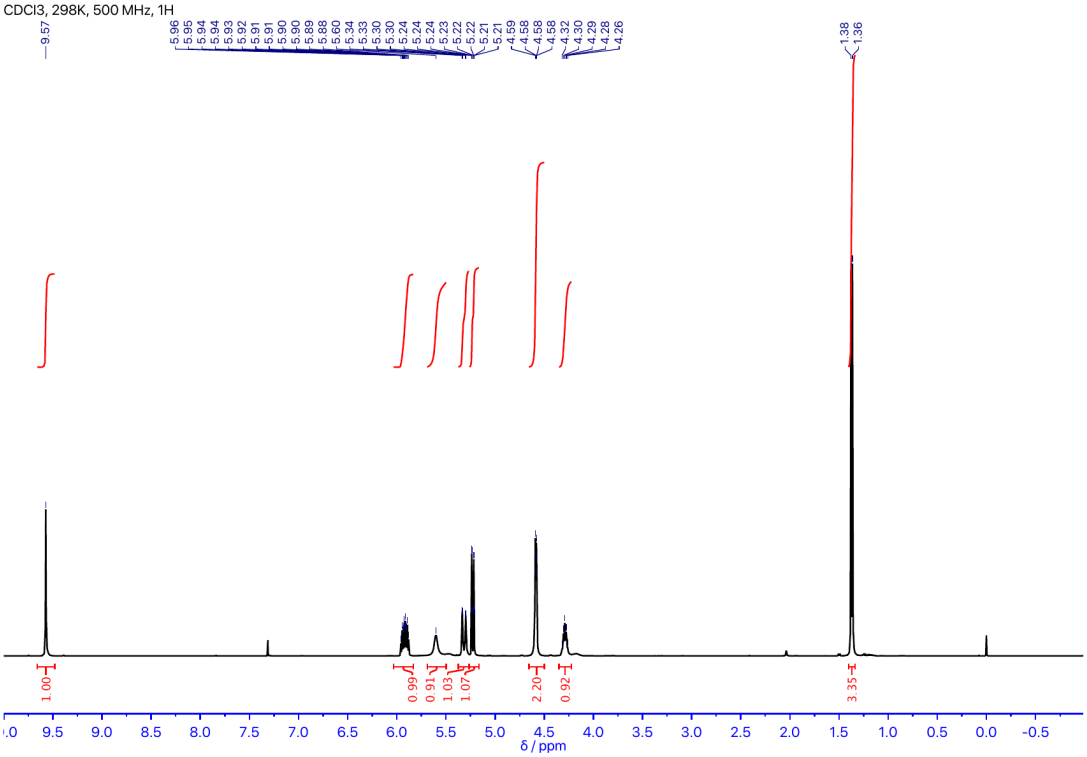


CDCl3, 298K, 126 MHz, 13C

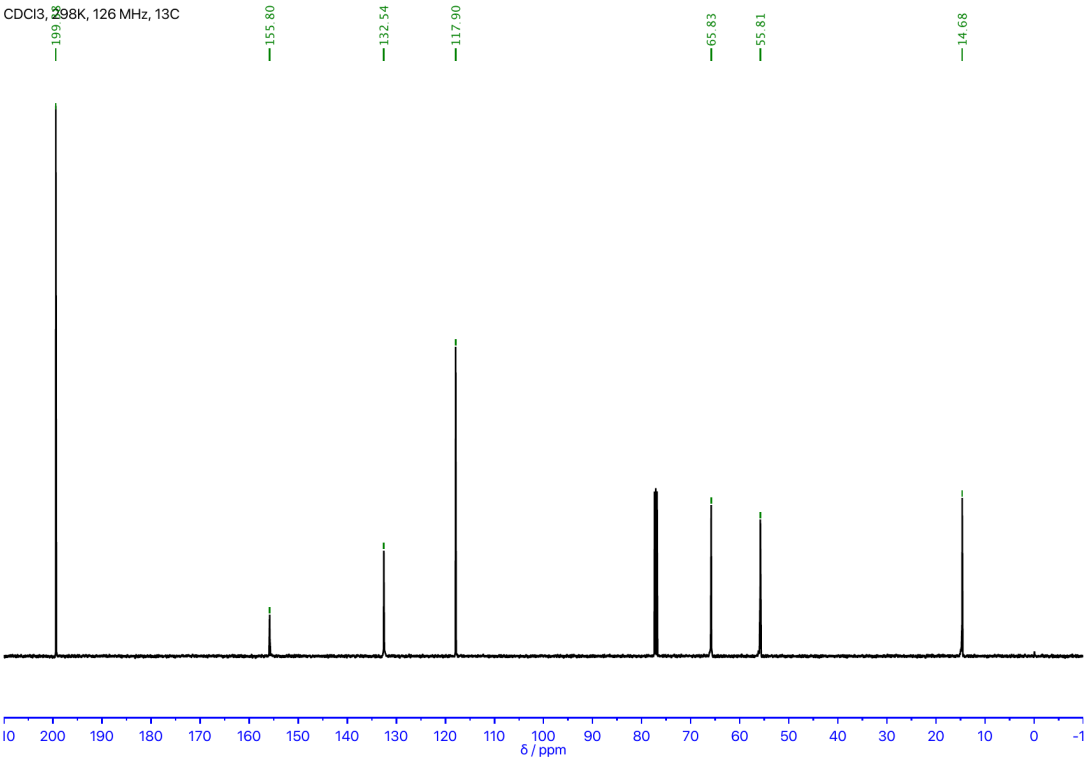


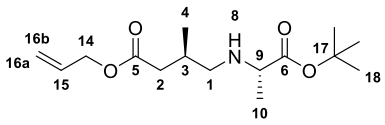


CDCl3, 298K, 500 MHz, 1H

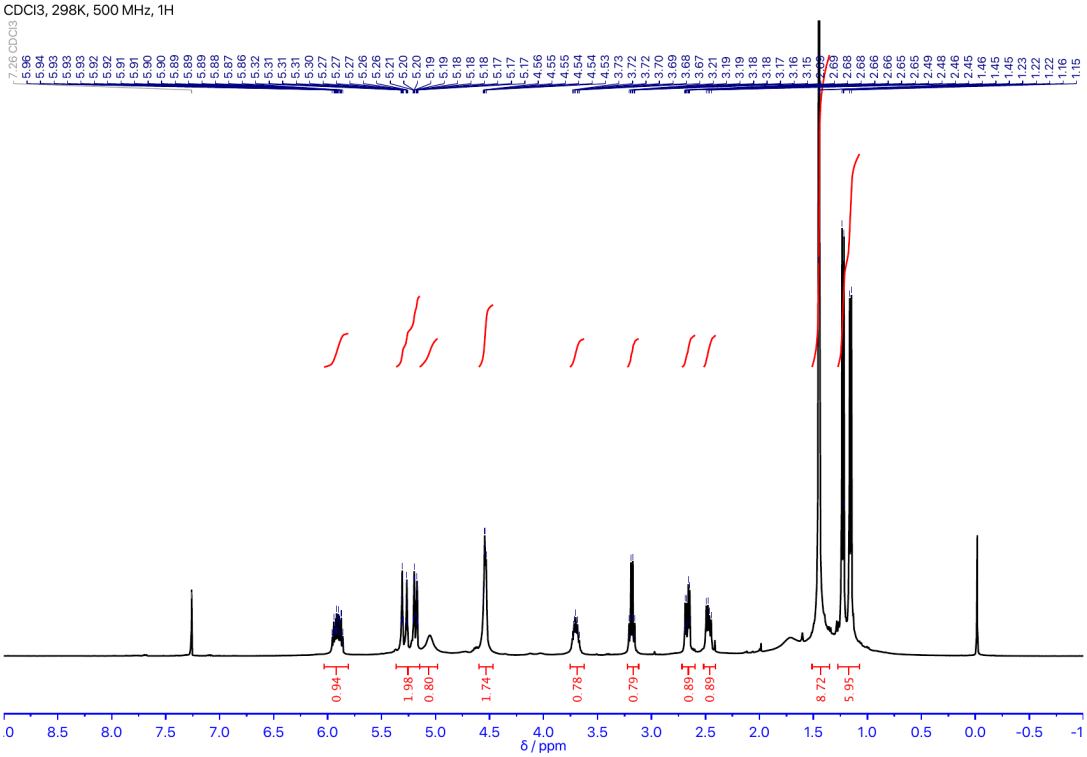


CDCl3, 298K, 126 MHz, 13C

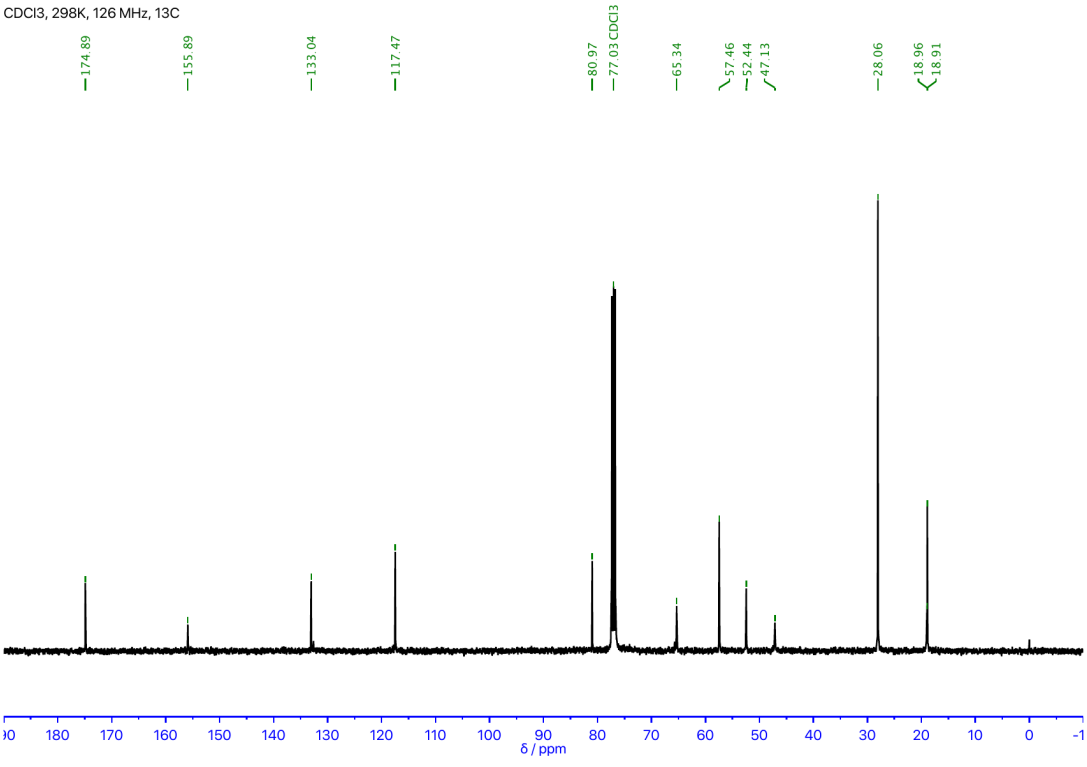


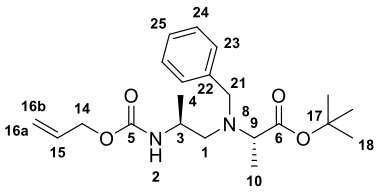


CDCl3, 298K, 500 MHz, 1H

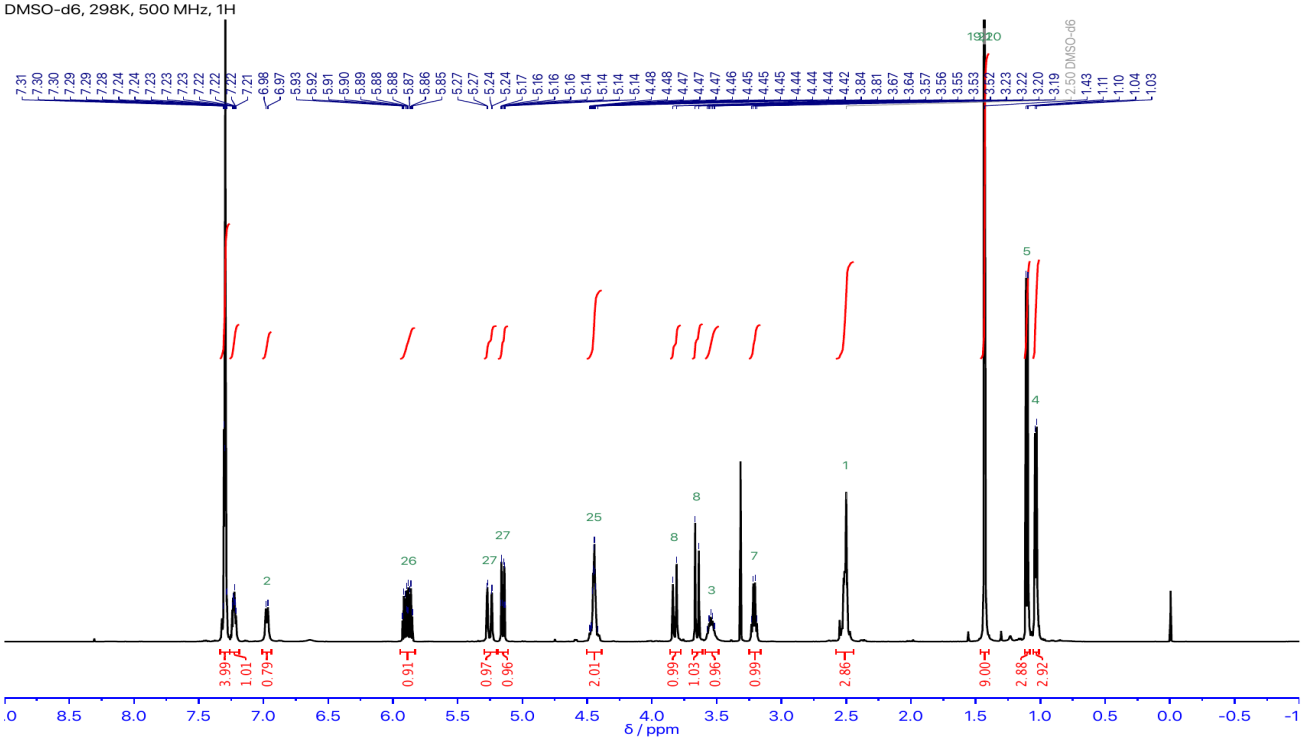


CDCl3, 298K, 126 MHz, 13C

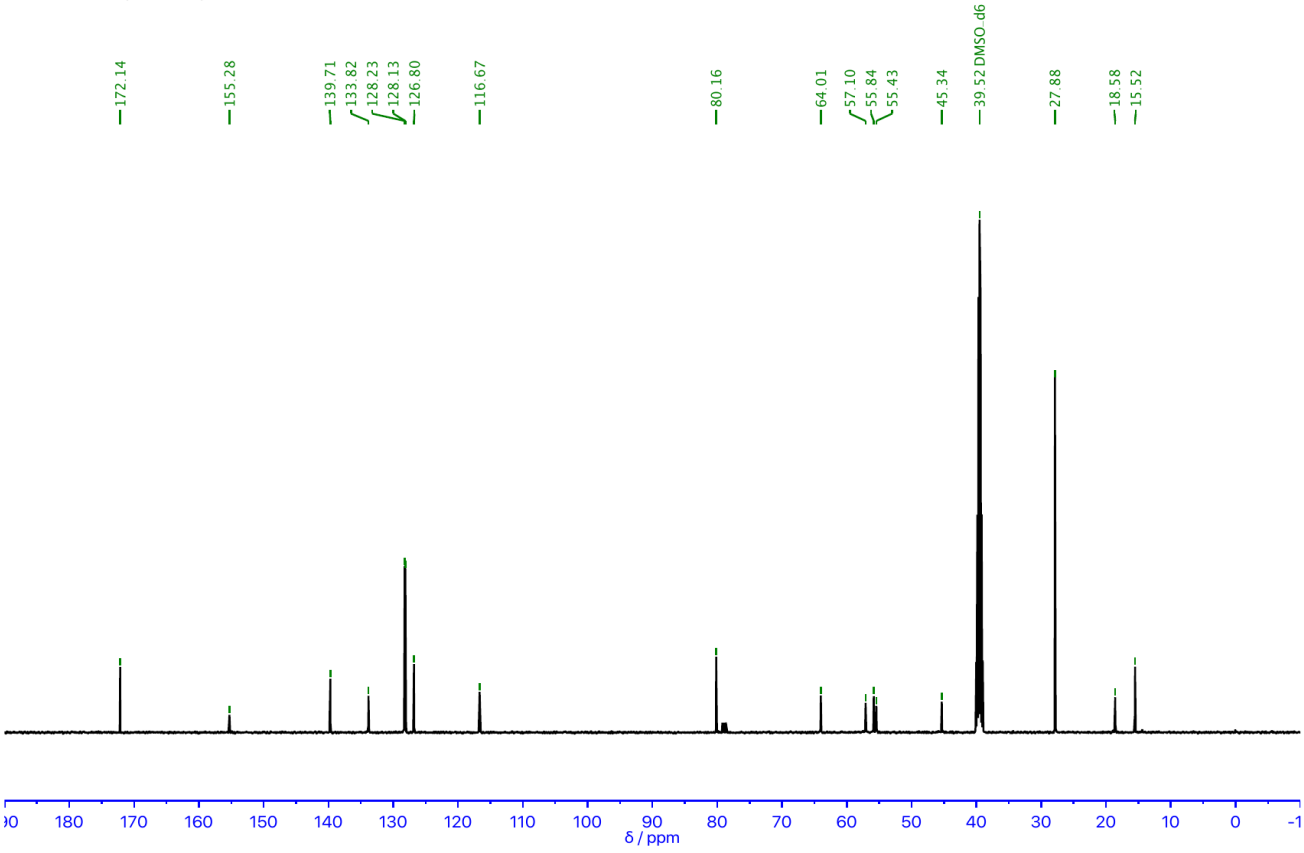


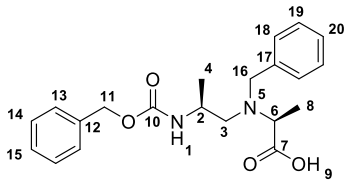


DMSO-d6, 298K, 500 MHz, 1H

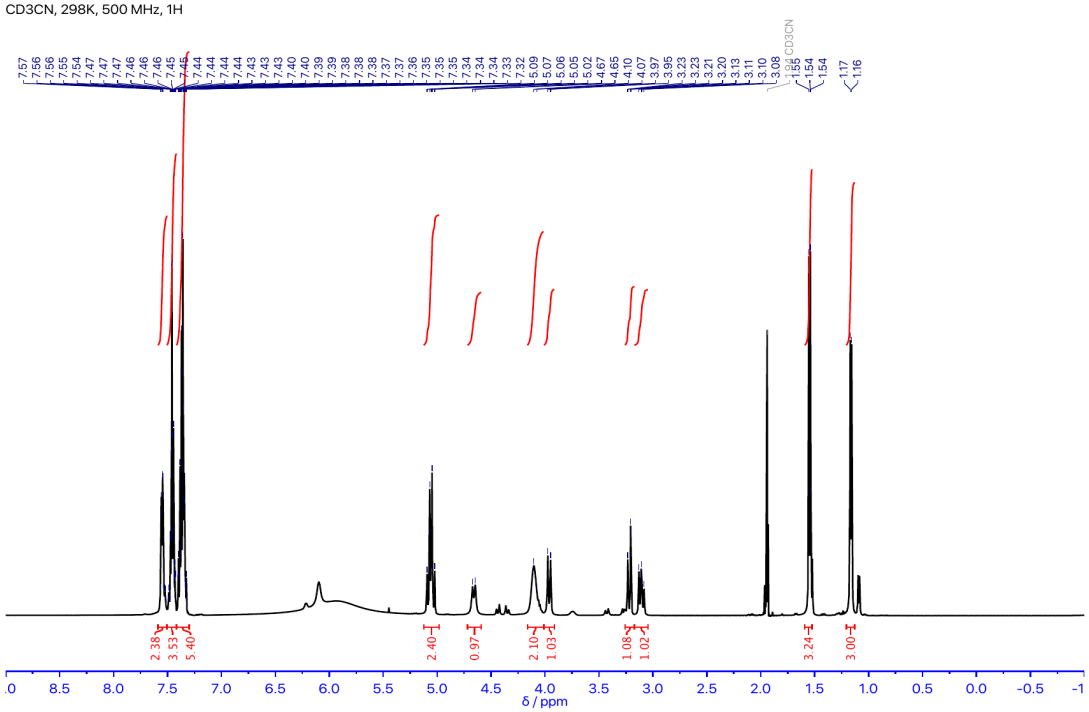


DMSO-d6 298K, 126 MHz, 13C

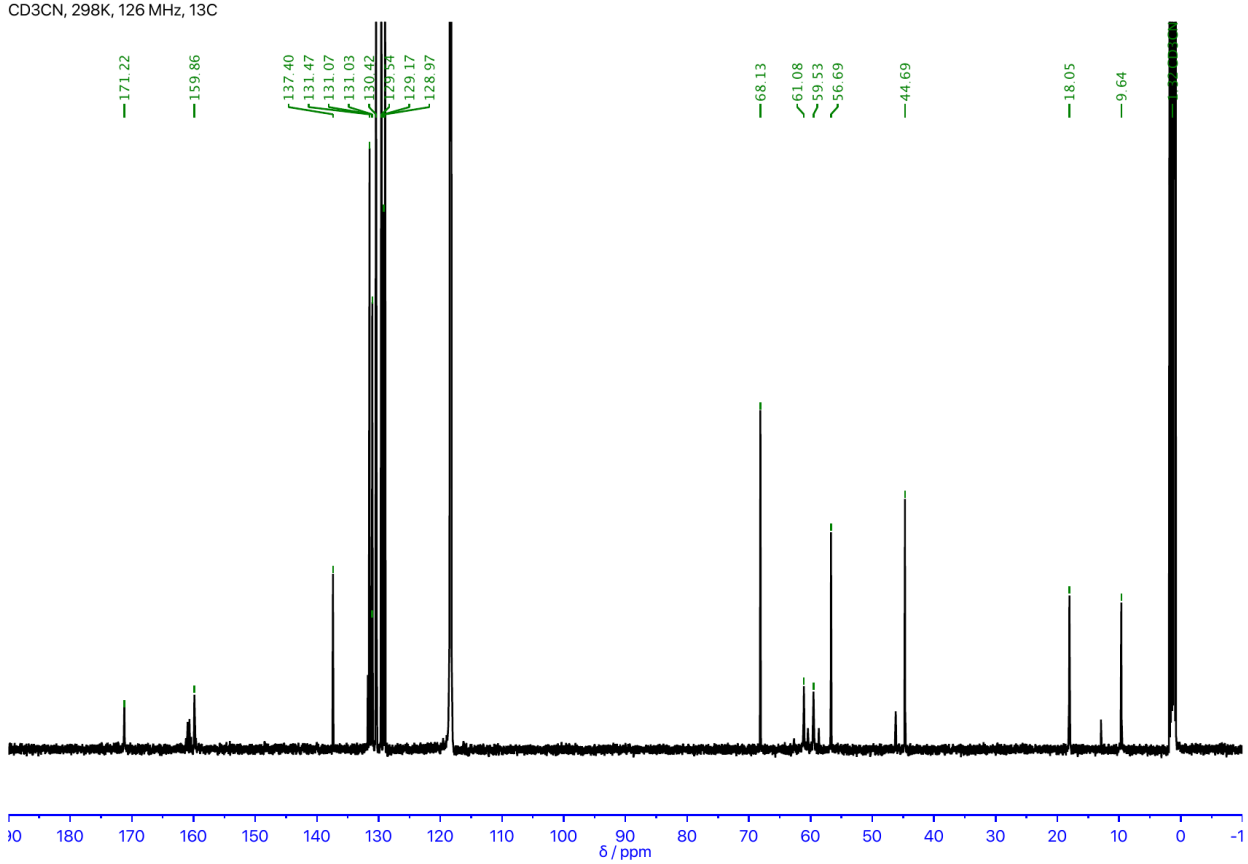


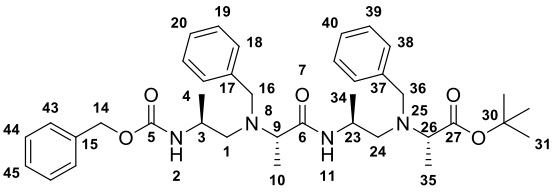


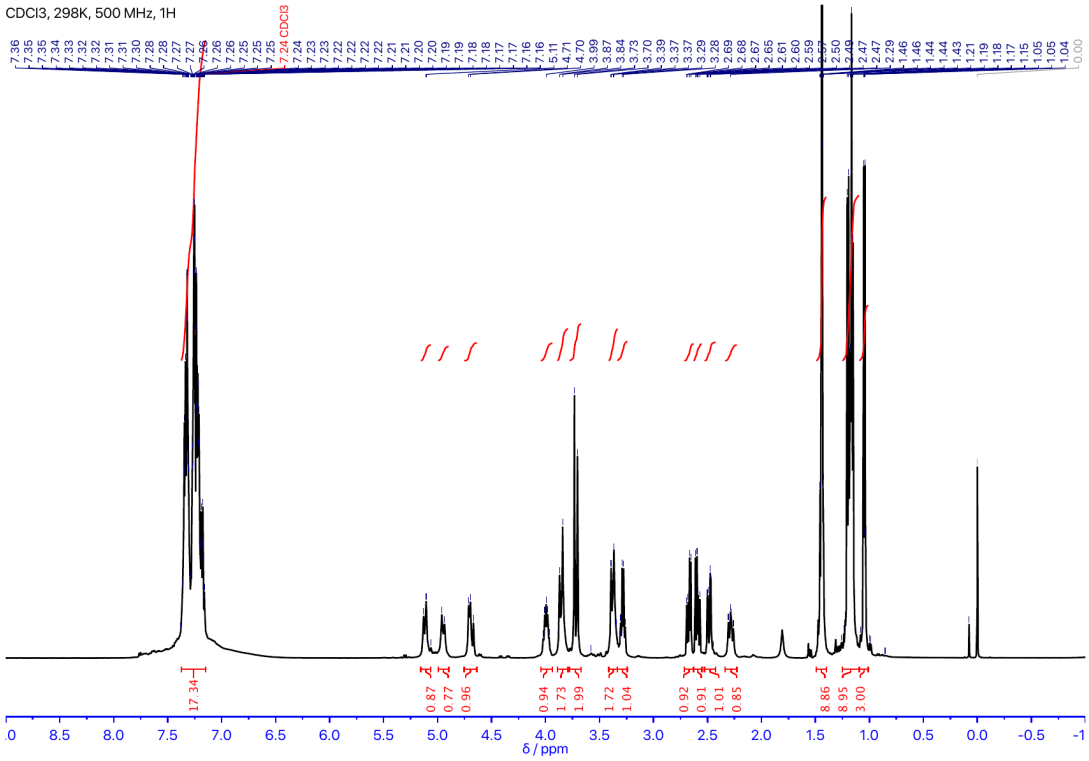
CD3CN, 298K, 500 MHz, 1H

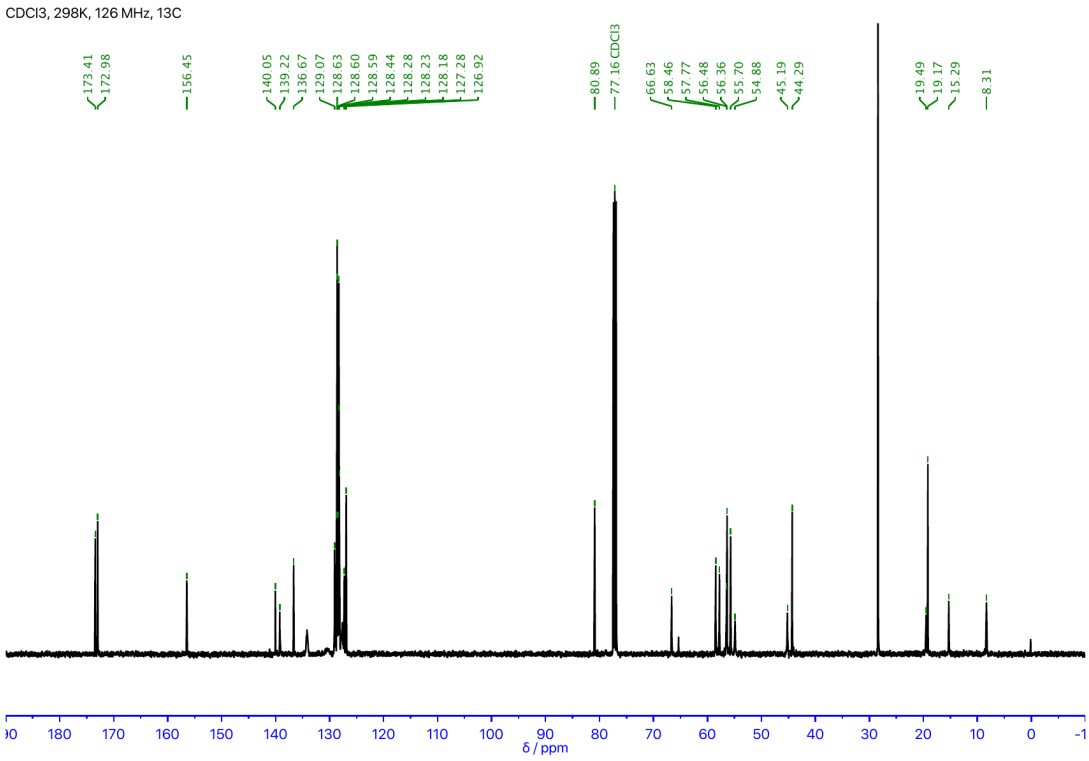


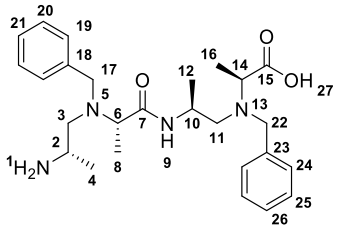
CD3CN, 298K, 126 MHz, 13C



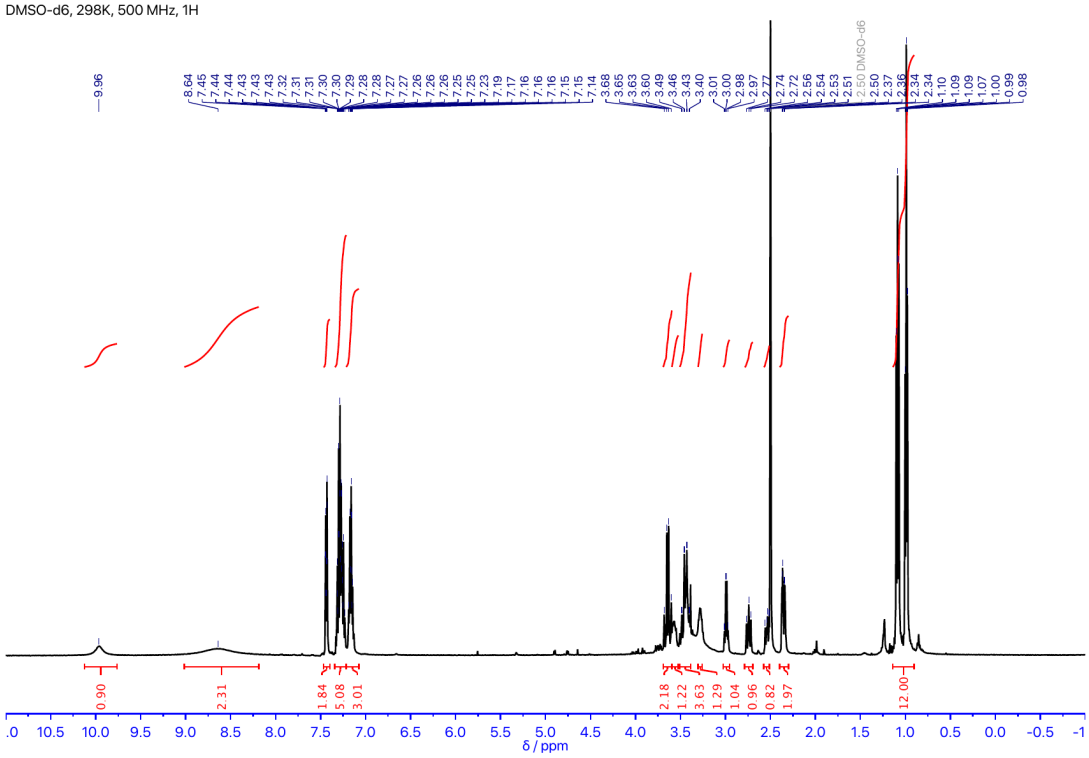



CDCl3, 298K, 500 MHz, 1H
δ / ppm

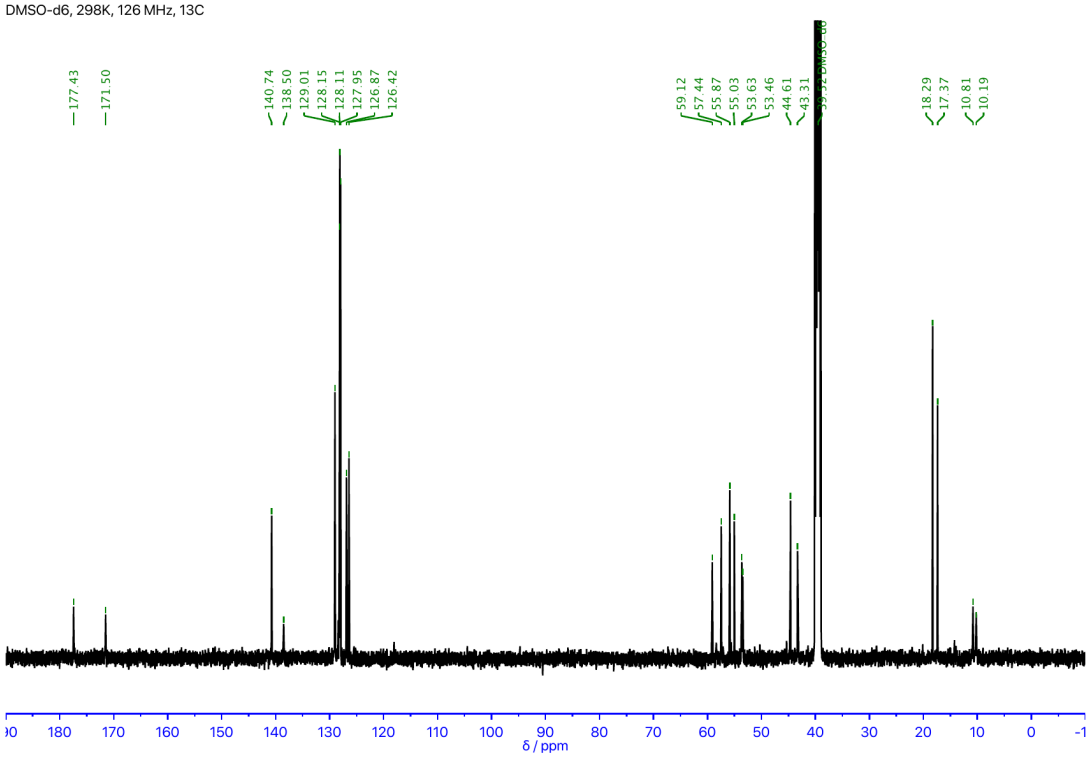

CDCl3, 298K, 126 MHz, 13C
δ / ppm

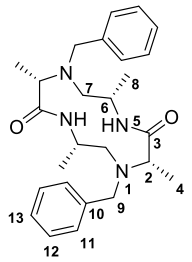


DMSO-d6, 298K, 500 MHz, 1H

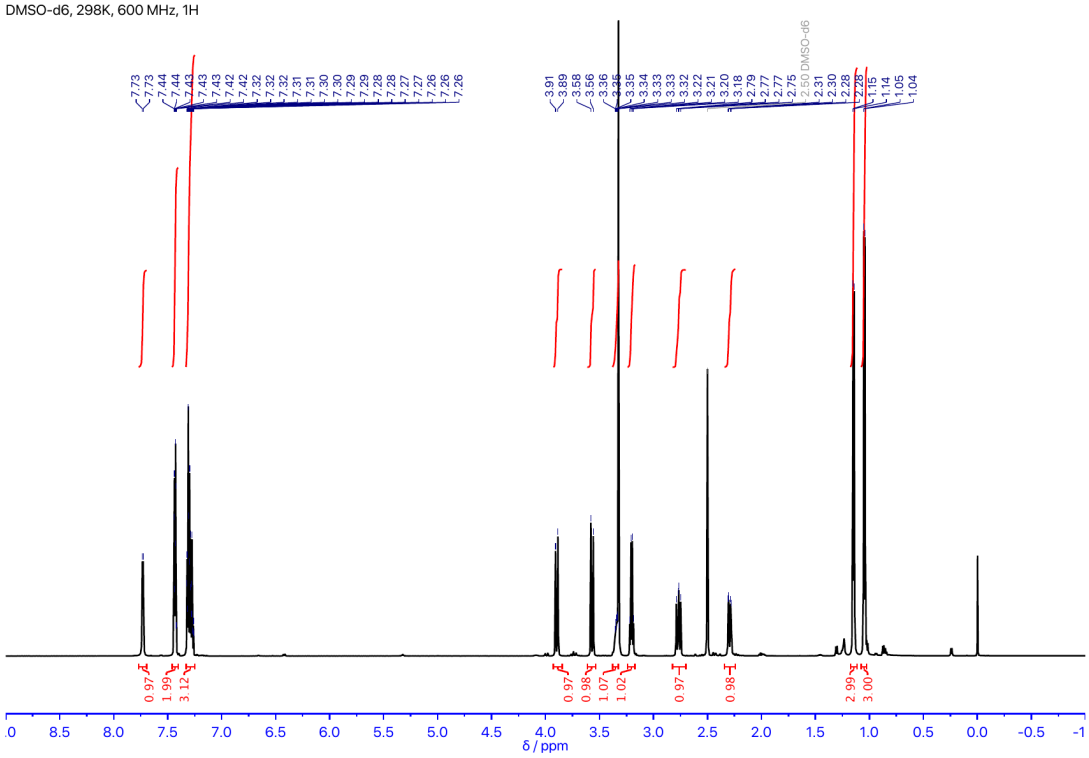


DMSO-d6, 298K, 126 MHz, 13C

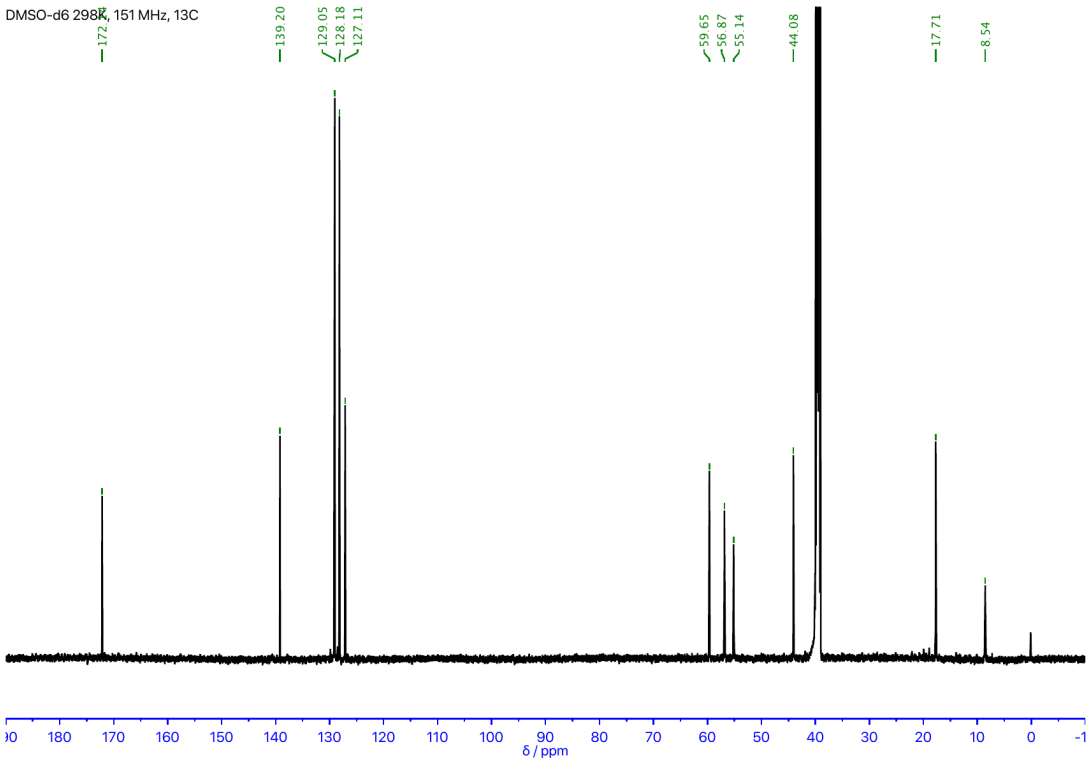


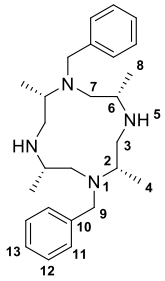


DMSO-d6, 298K, 600 MHz, 1H

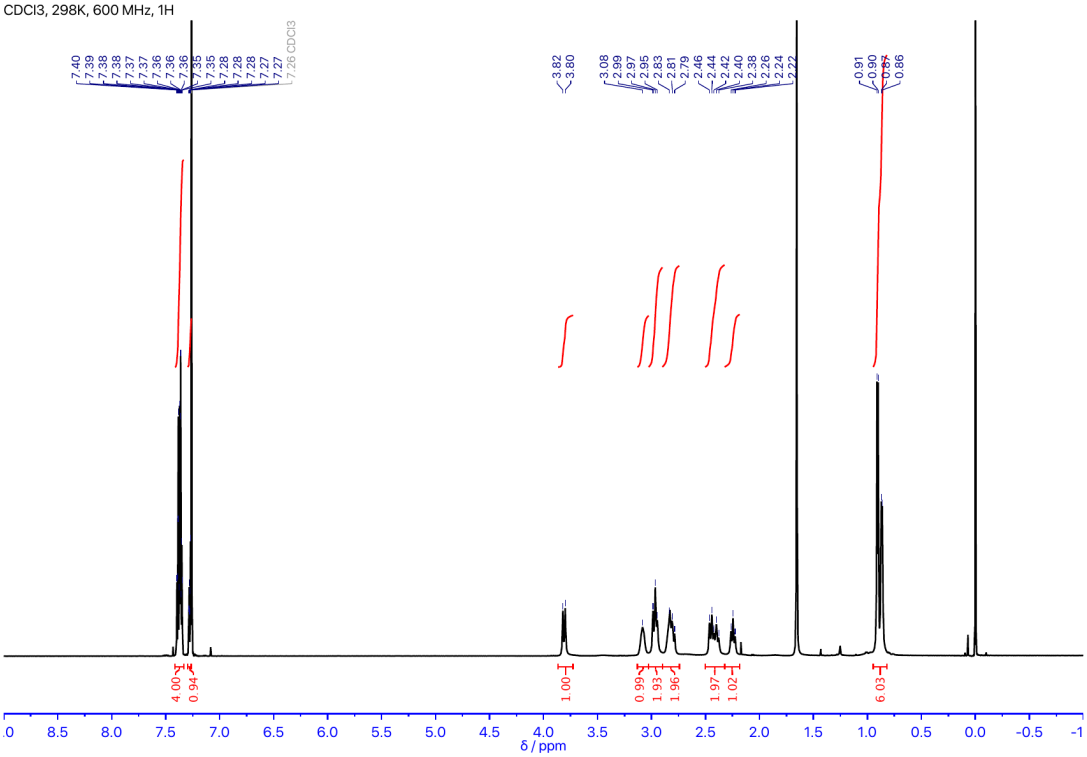


DMSO-d6 298K, 151 MHz, 13C

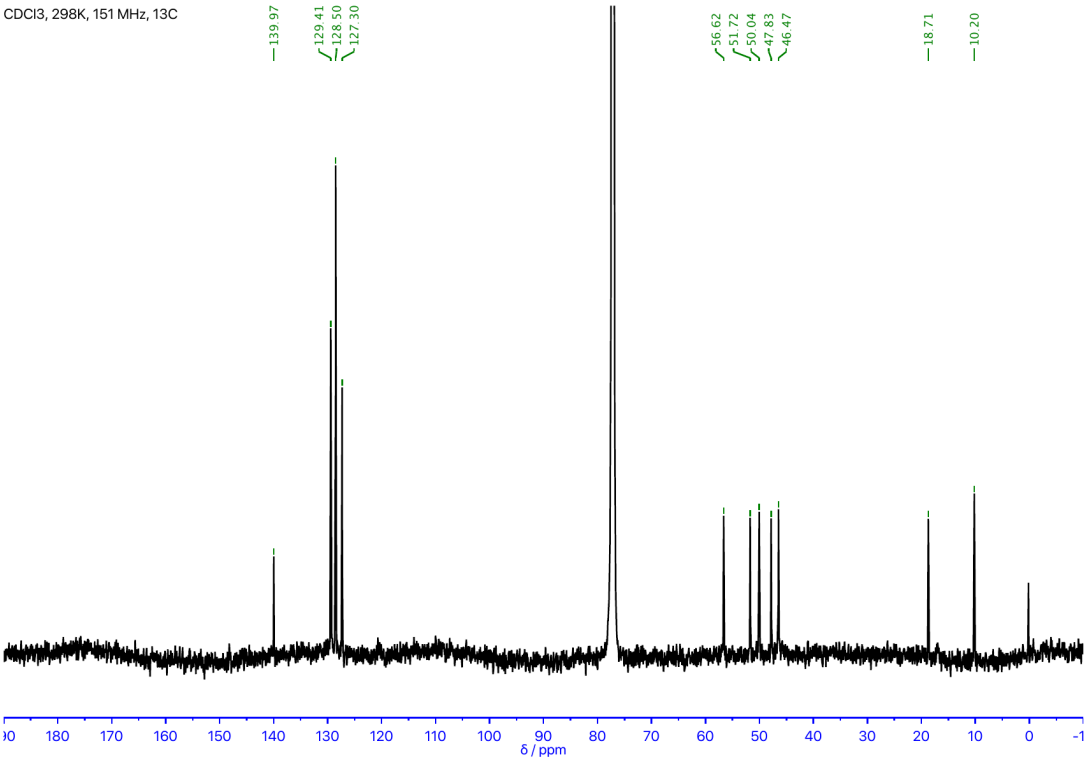


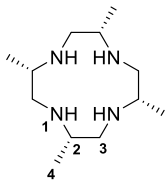


CDCl3, 298K, 600 MHz, 1H

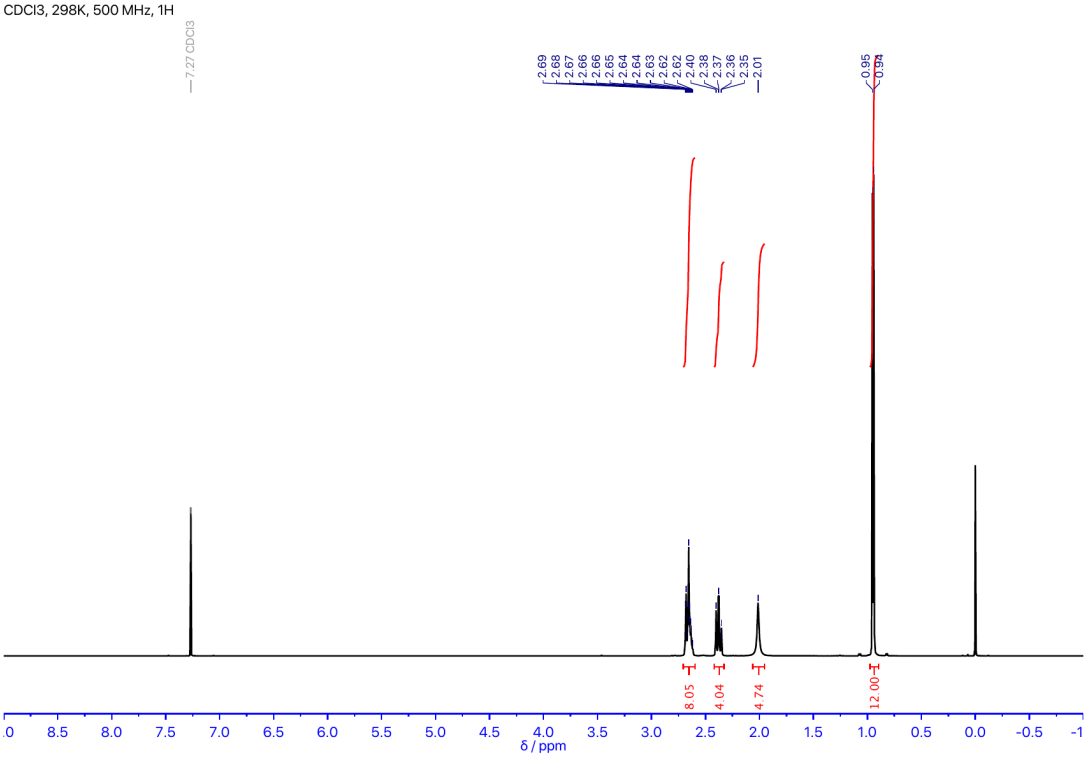


CDCl3, 298K, 151 MHz, 13C

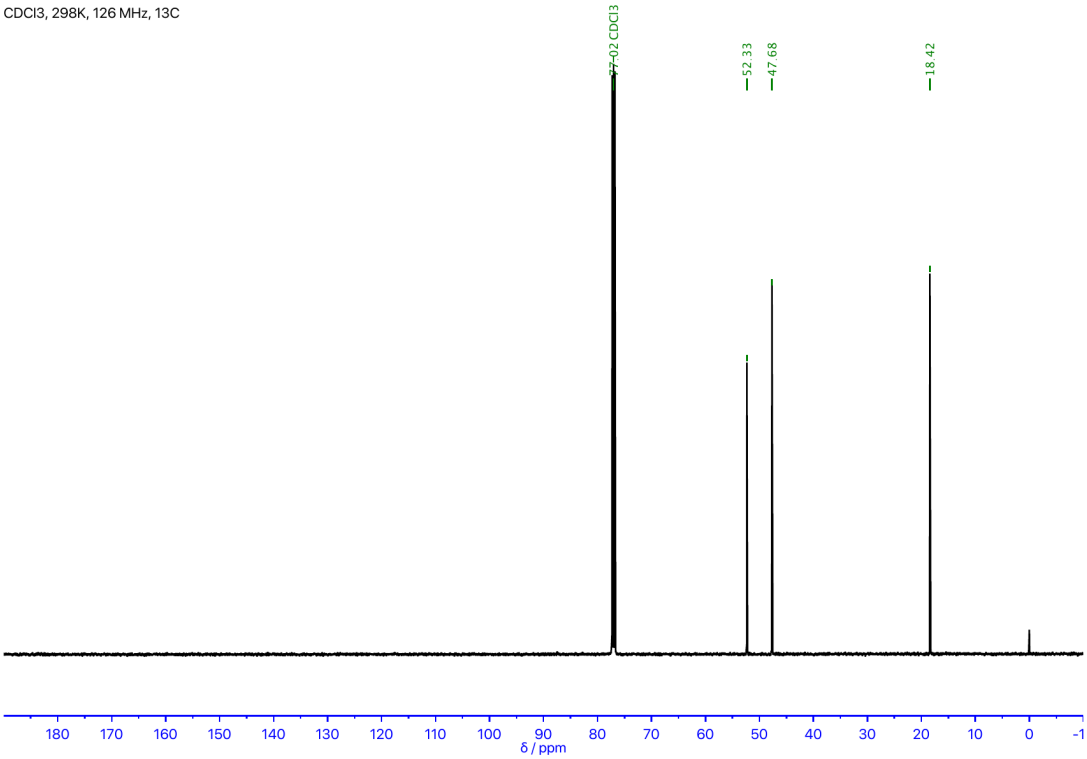


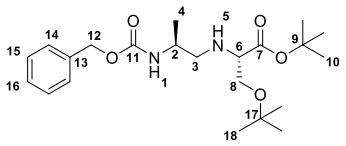


CDCl3, 298K, 500 MHz, 1H

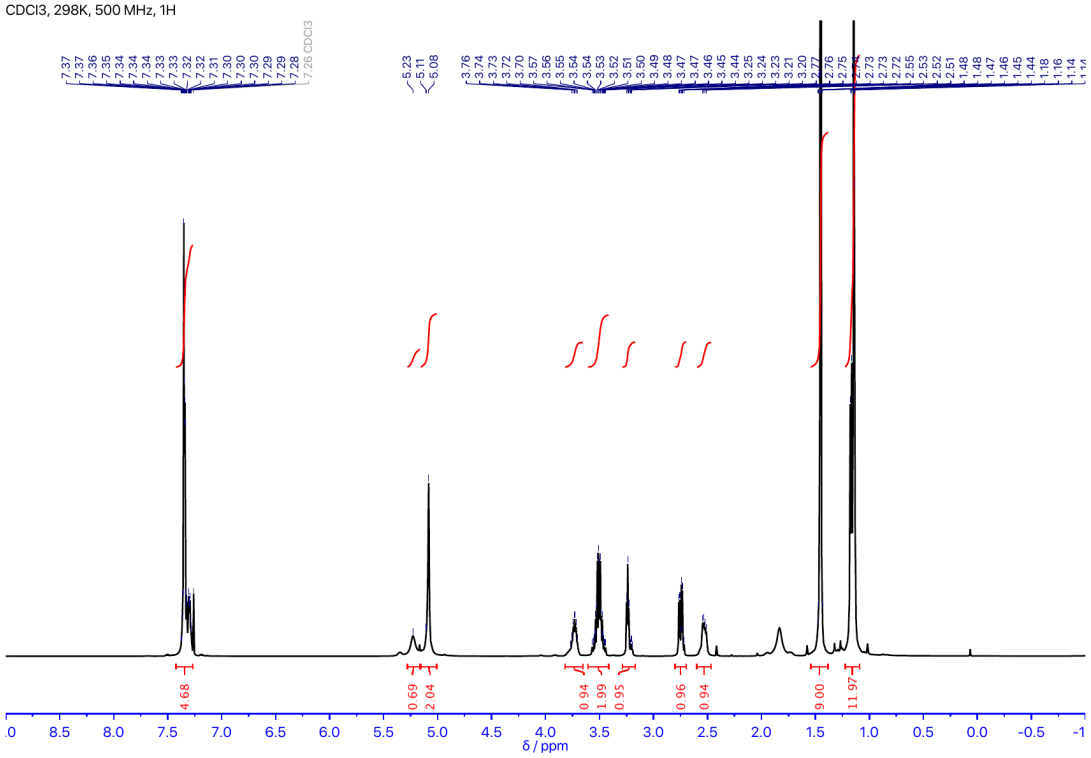


CDCl3, 298K, 126 MHz, 13C

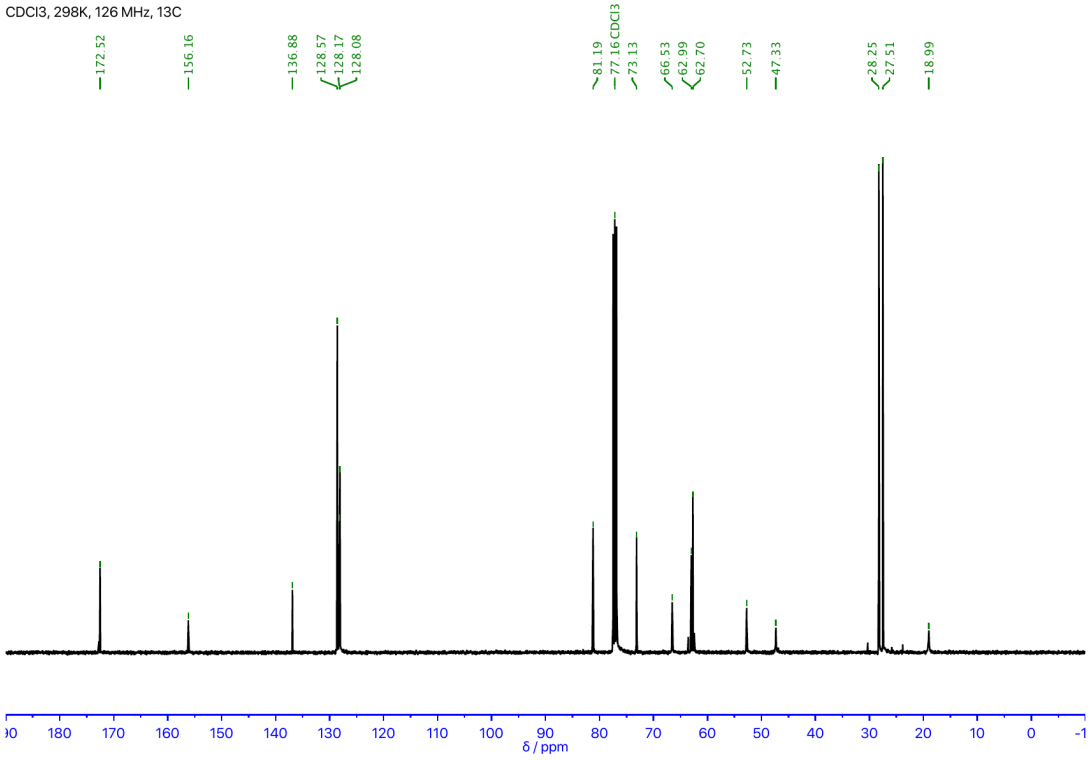


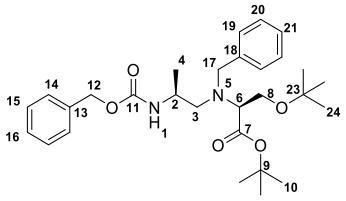


CDCl3, 298K, 500 MHz, 1H

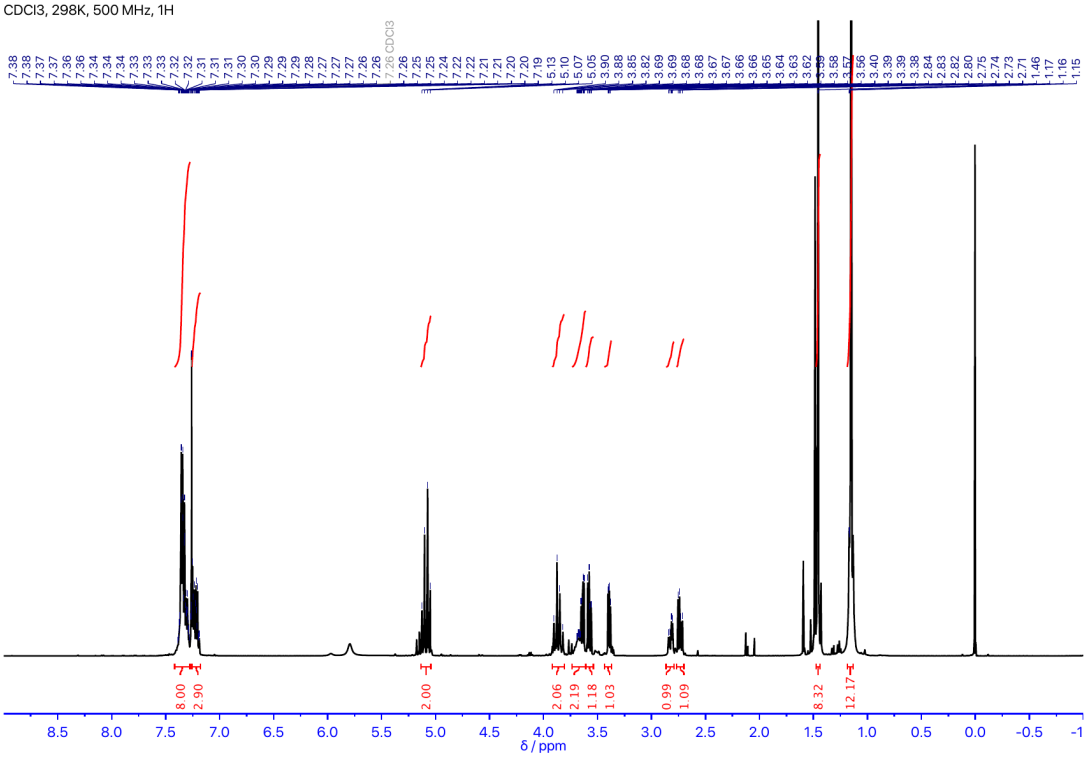


CDCl3, 298K, 126 MHz, 13C

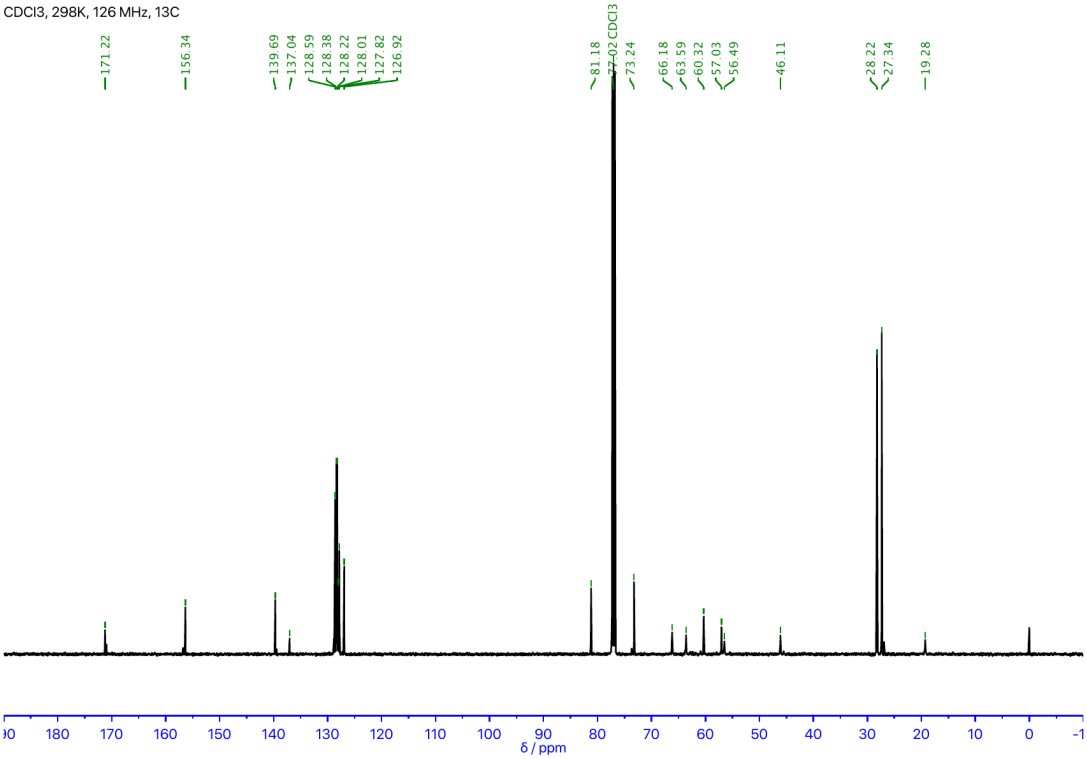


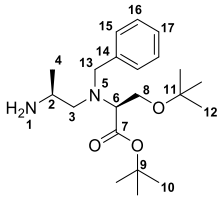


CDCl3, 298K, 500 MHz, 1H

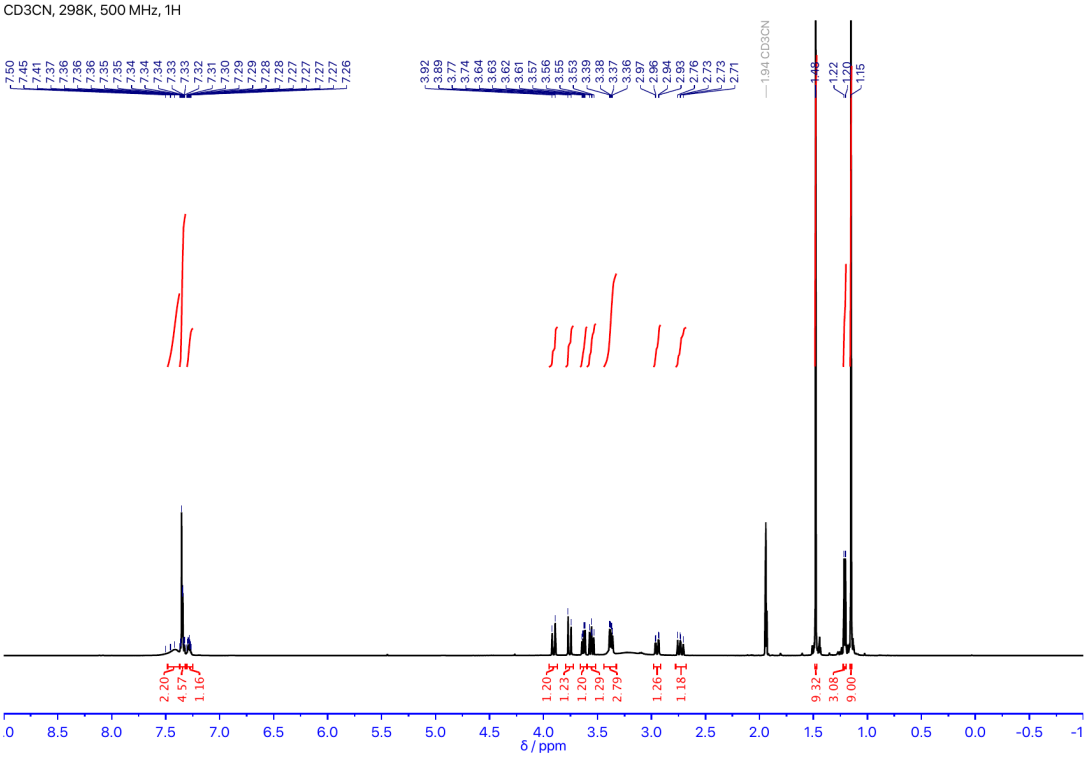


CDCl3, 298K, 126 MHz, 13C

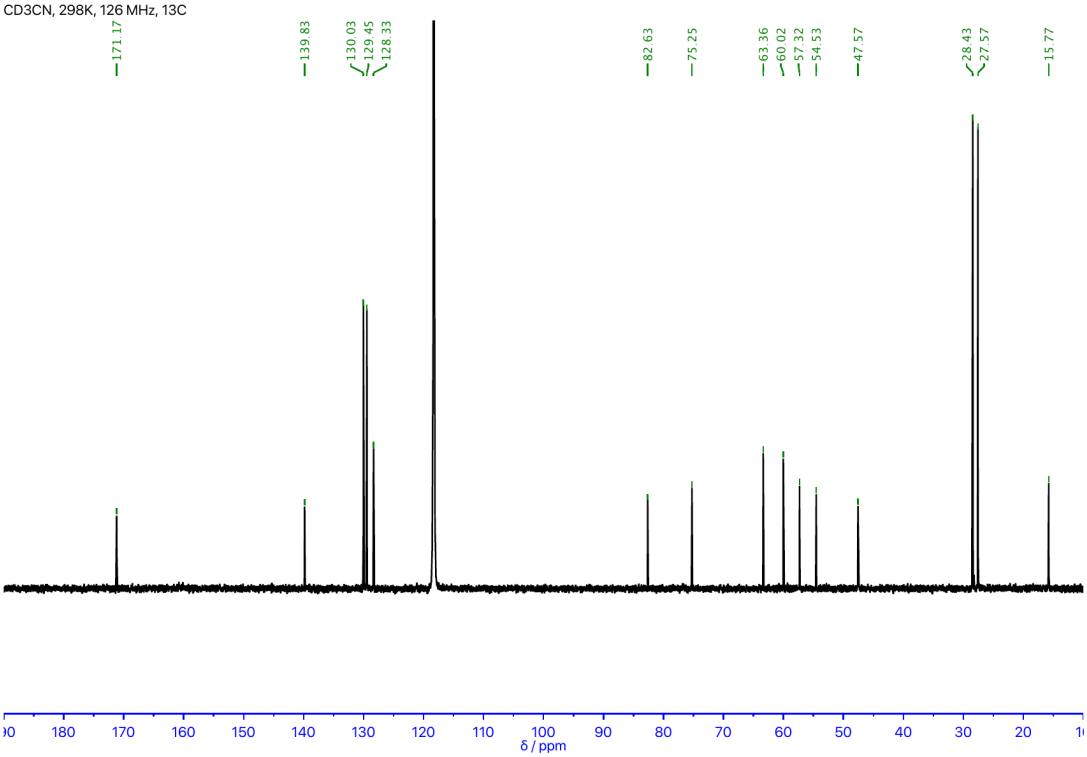


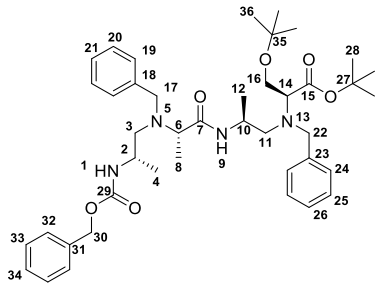


CD3CN, 298K, 500 MHz, 1H

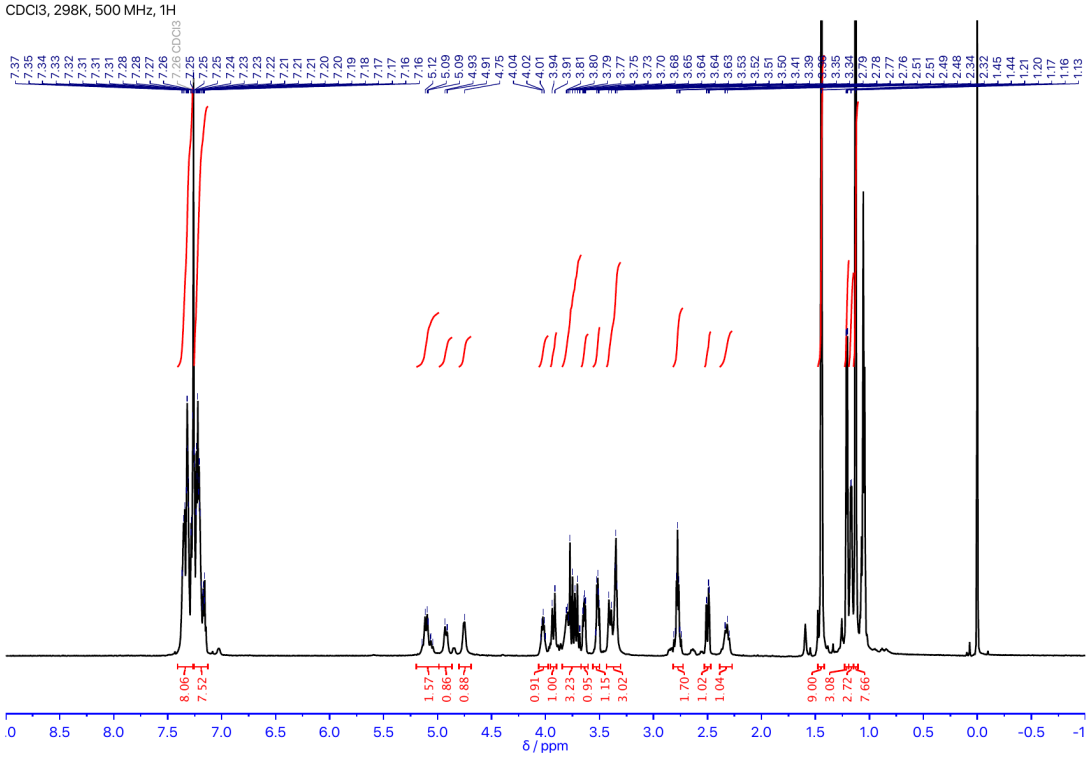


CD3CN, 298K, 126 MHz, 13C

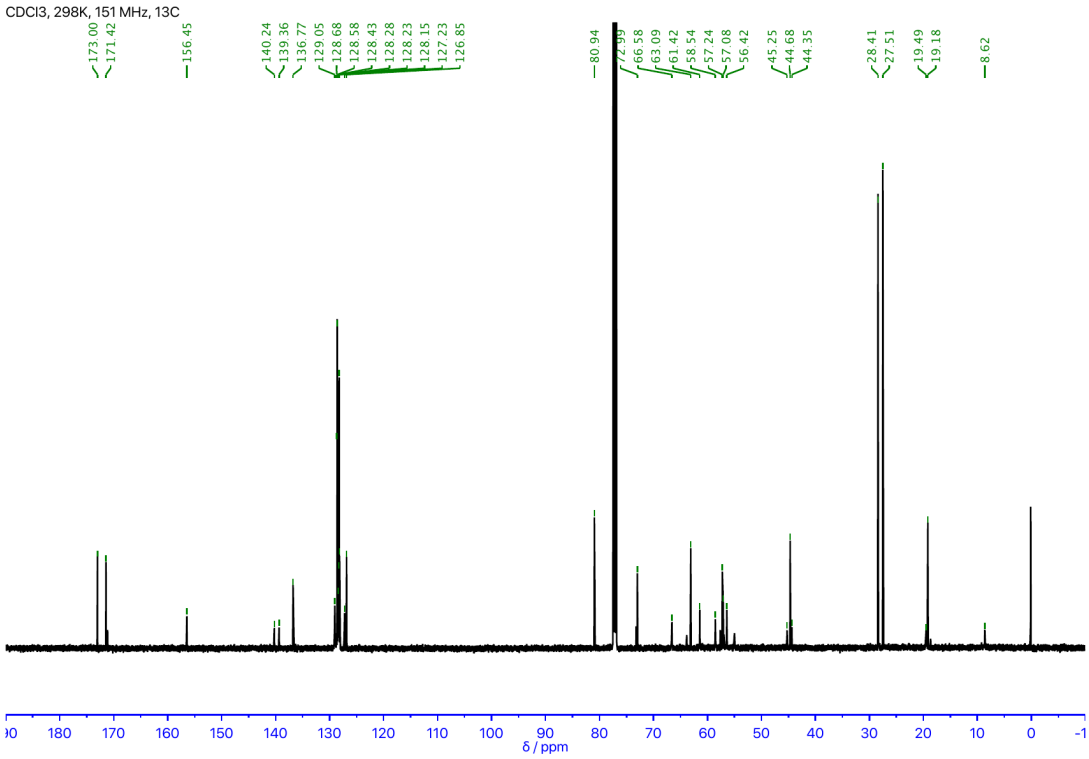


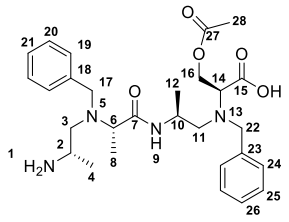


CDCl3, 298K, 500 MHz, 1H

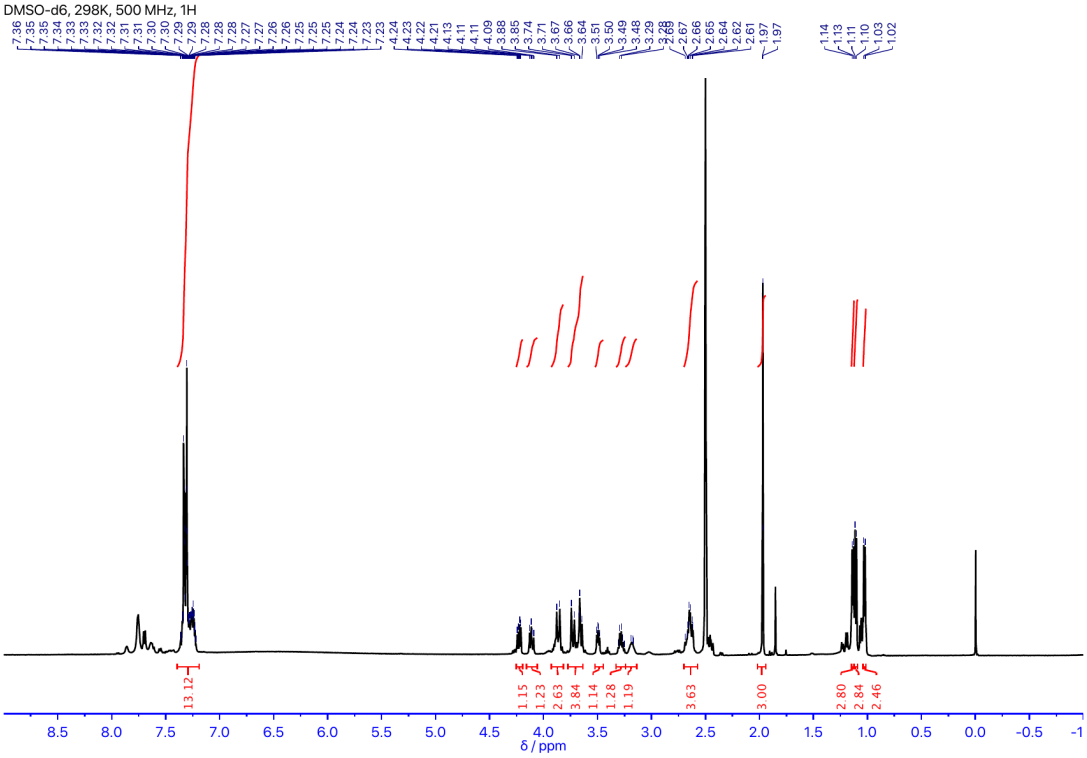


CDCl3, 298K, 151 MHz, 13C

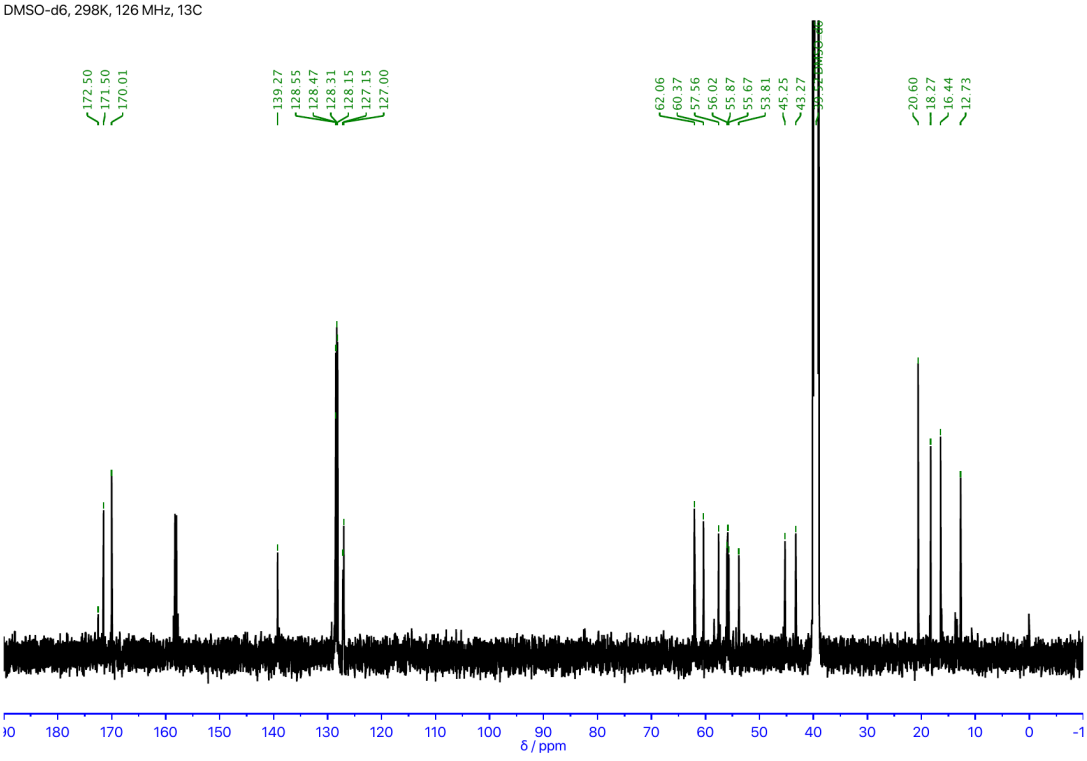


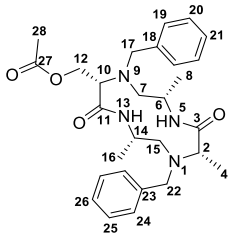


DMSO-d6, 298K, 500 MHz, 1H

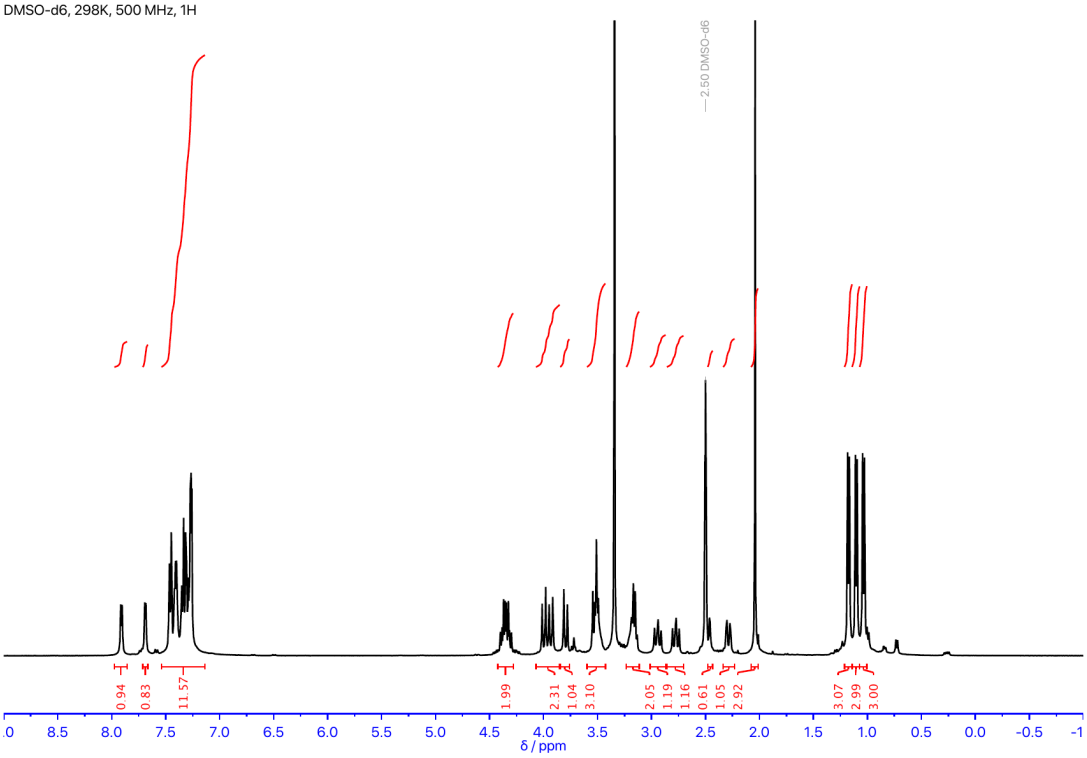


DMSO-d6, 298K, 126 MHz, 13C

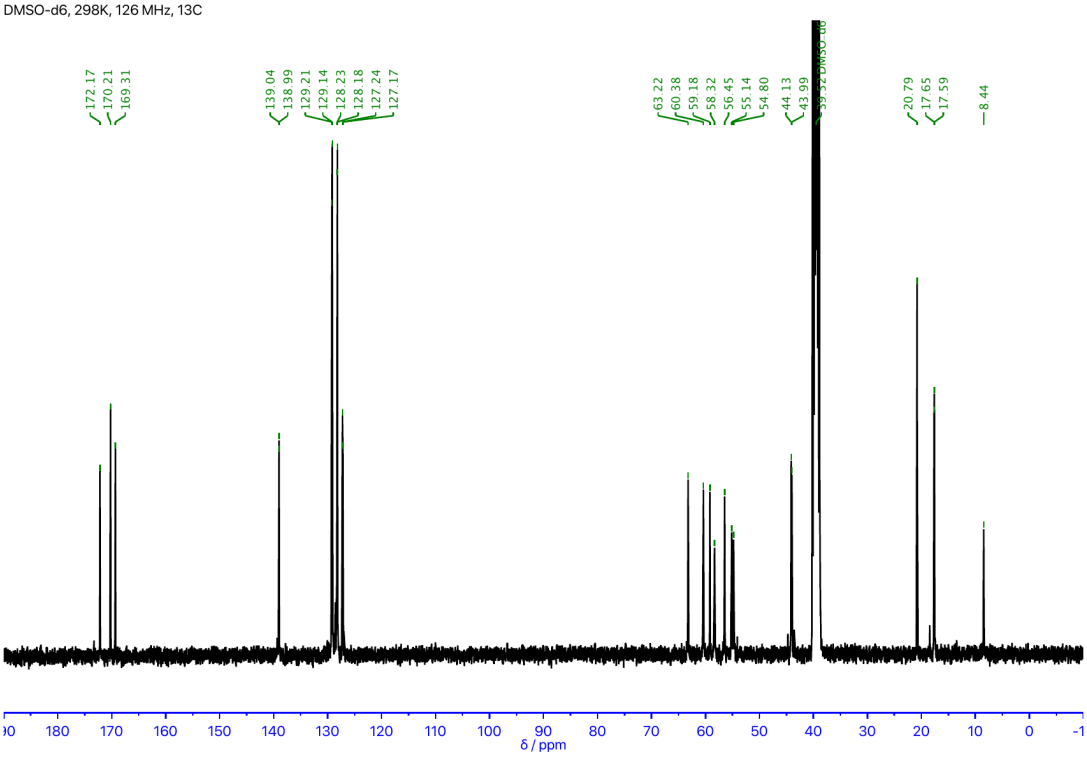


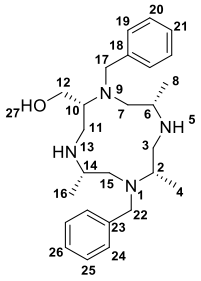


DMSO-d6, 298K, 500 MHz, 1H

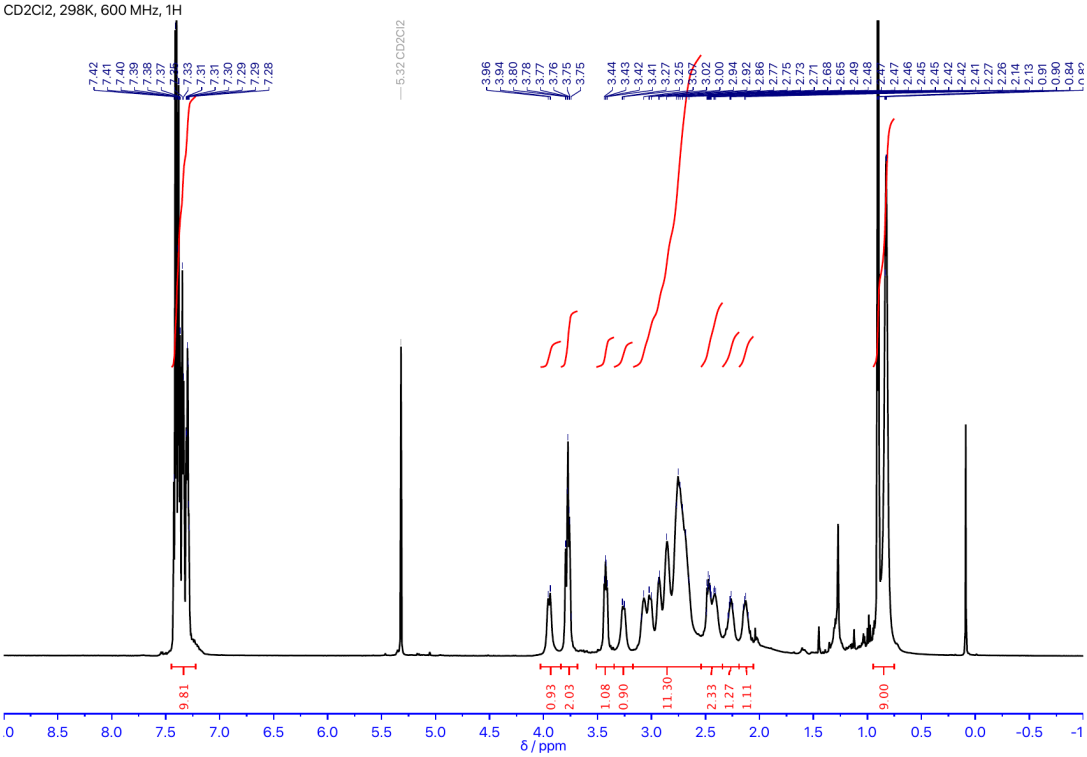


DMSO-d6, 298K, 126 MHz, 13C

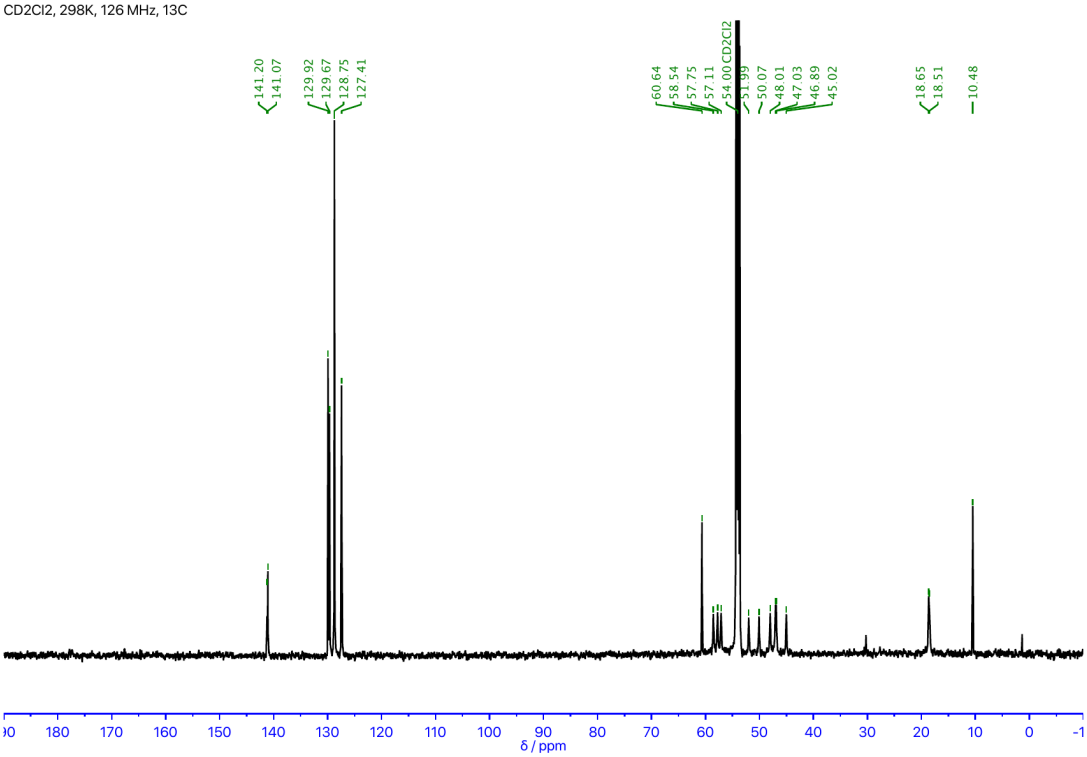


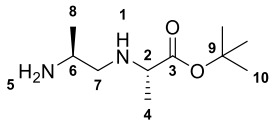


CD2Cl2, 298K, 600 MHz, 1H

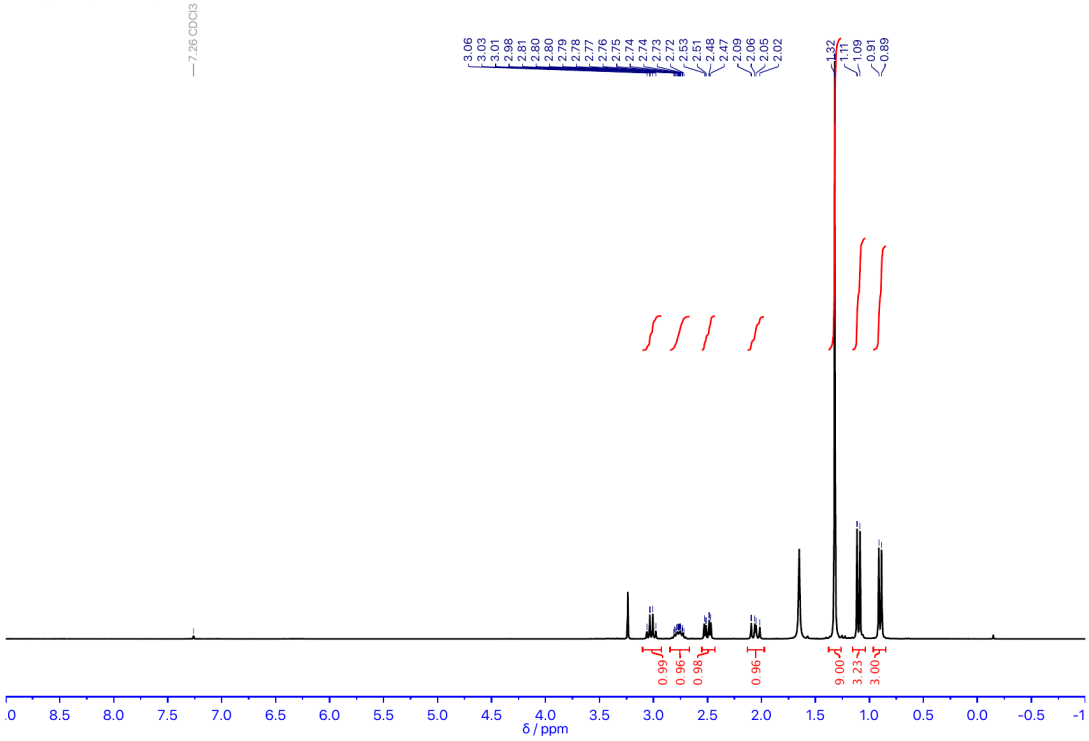


CD2Cl2, 298K, 126 MHz, 13C

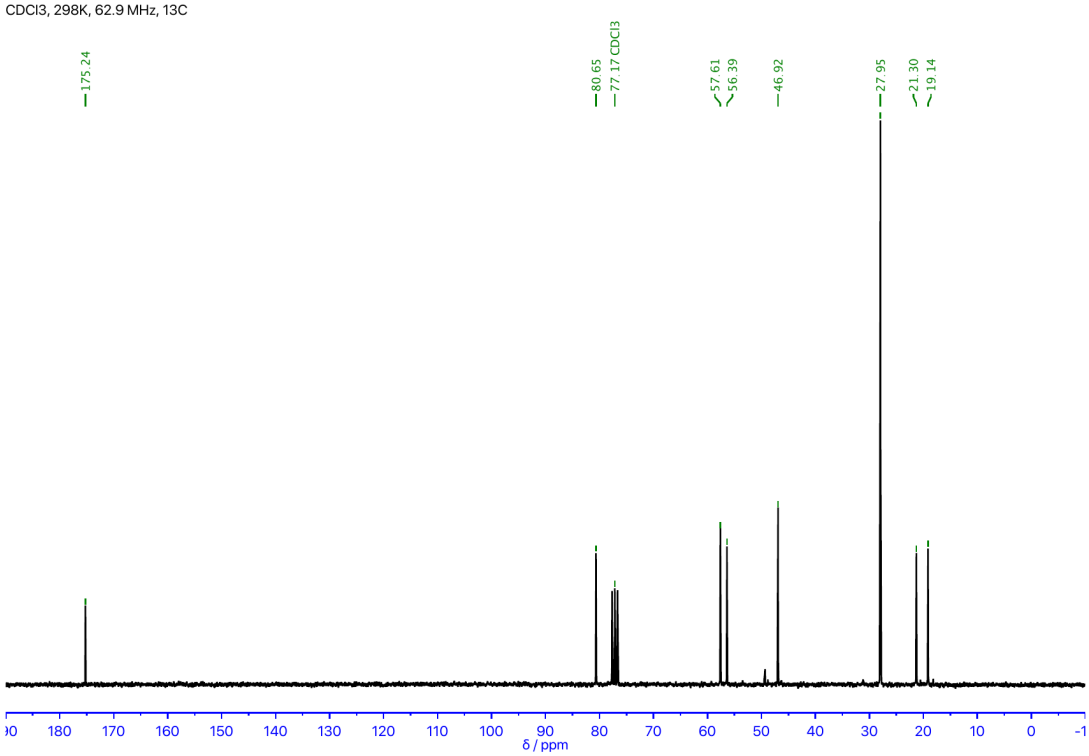


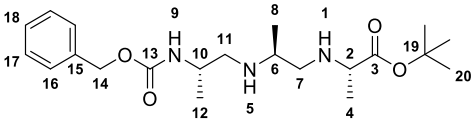


CDCl3, 298K, 250 MHz, 1H

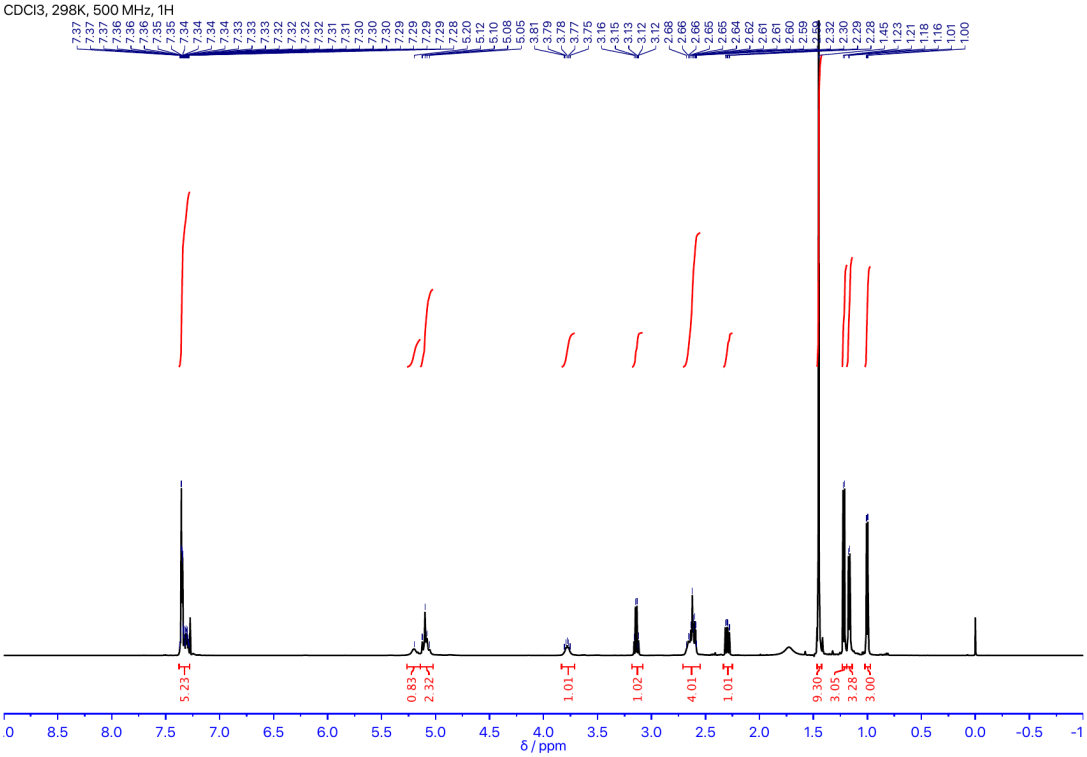


CDCl3, 298K, 62.9 MHz, 13C

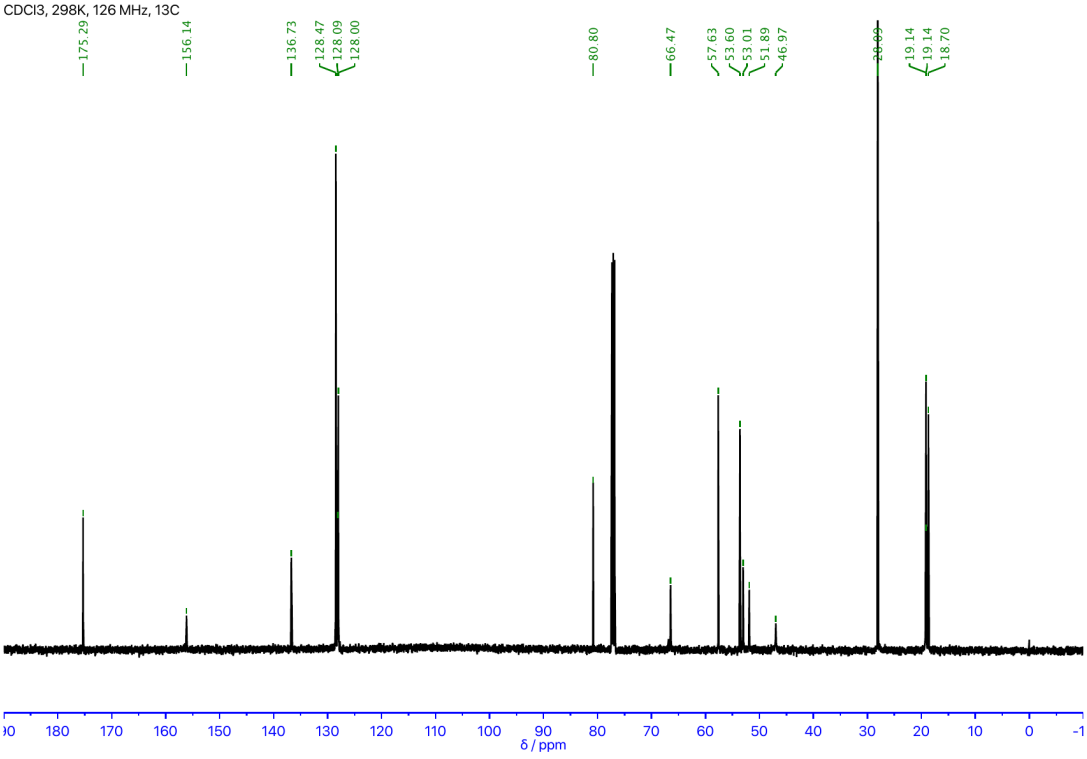


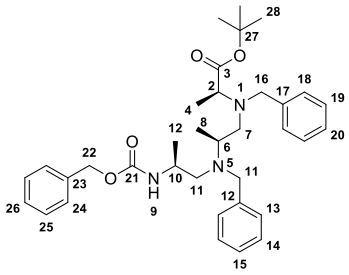


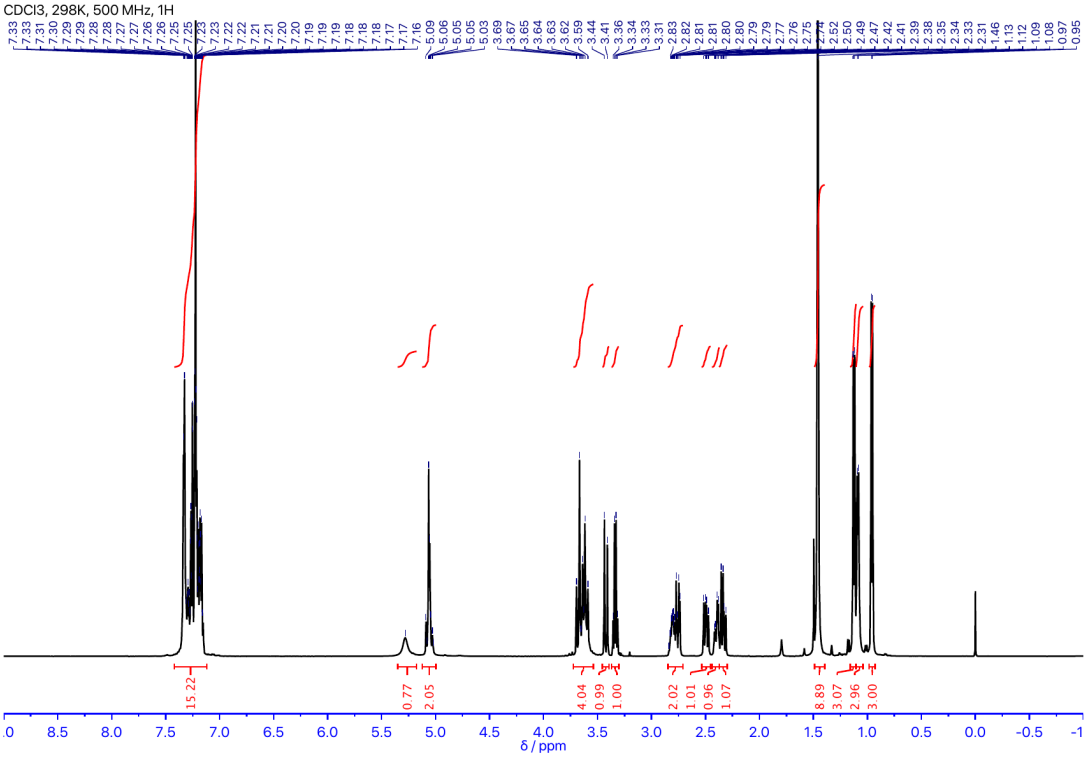
CDCl3, 298K, 500 MHz, 1H

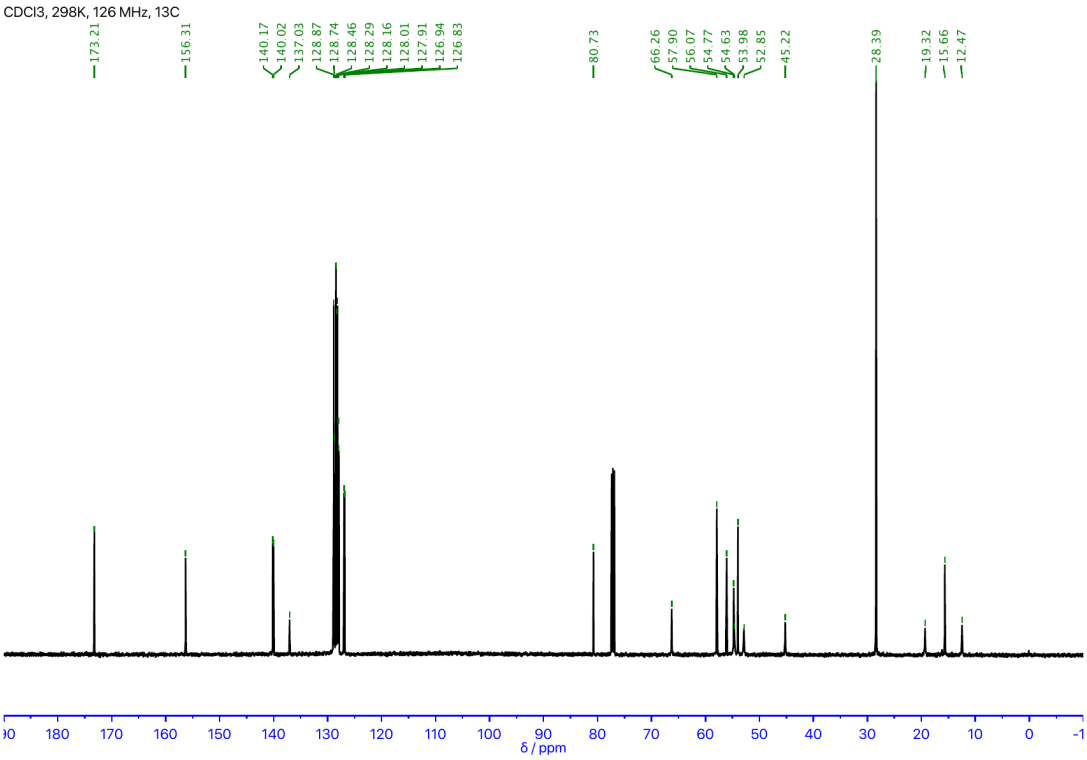


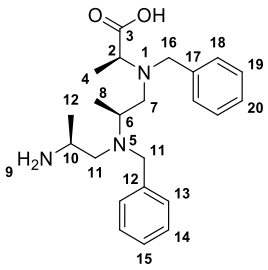
CDCl3, 298K, 126 MHz, 13C



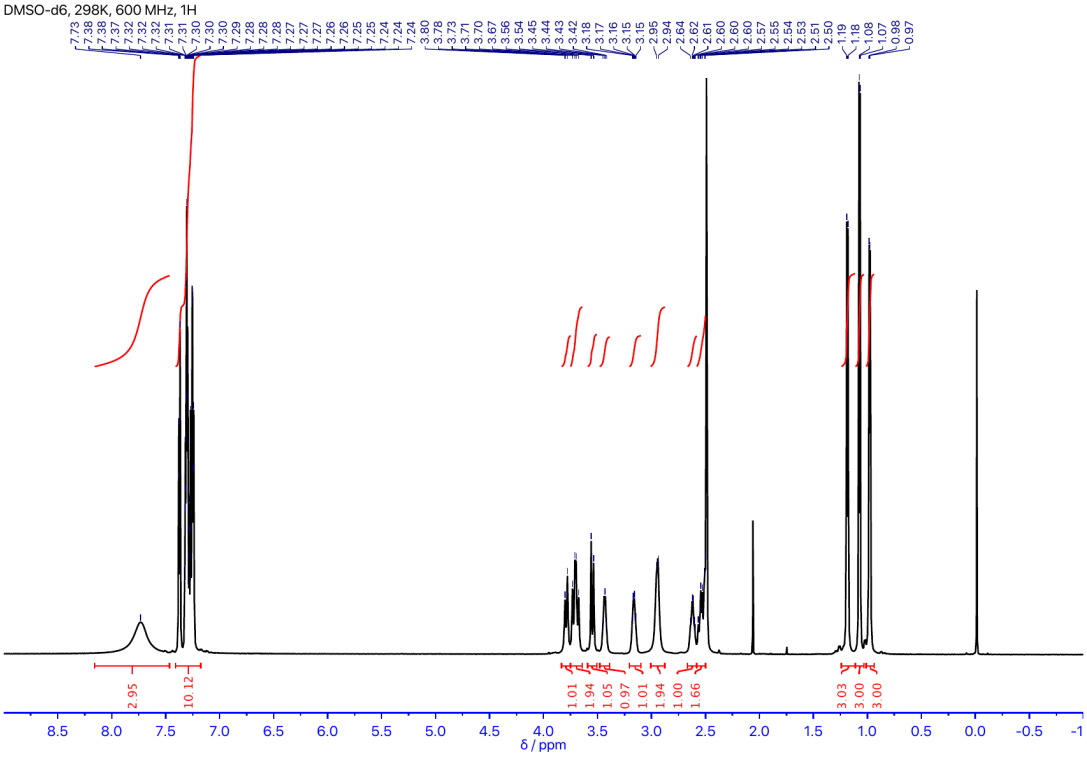



CDCl3, 298K, 500 MHz, 1H
δ / ppm

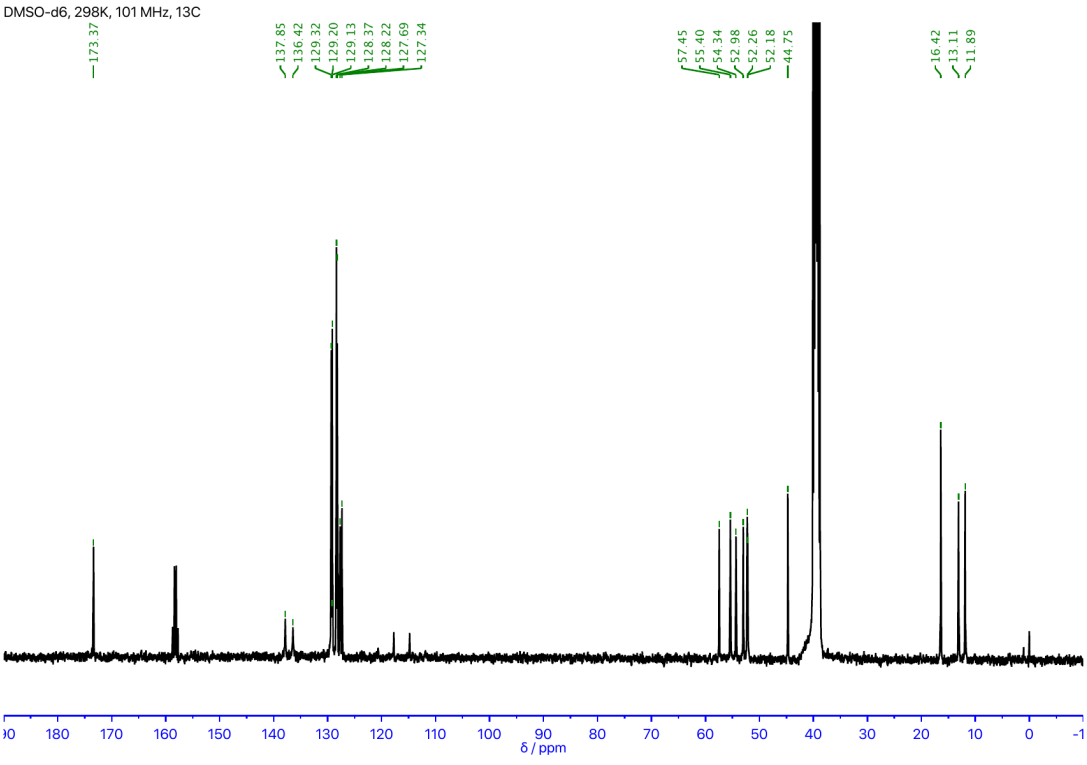

CDCl3, 298K, 126 MHz, 13C
δ / ppm

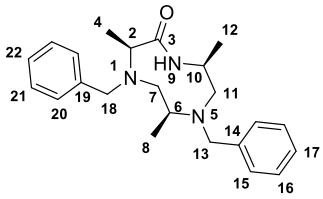


DMSO-d6, 298K, 600 MHz, 1H

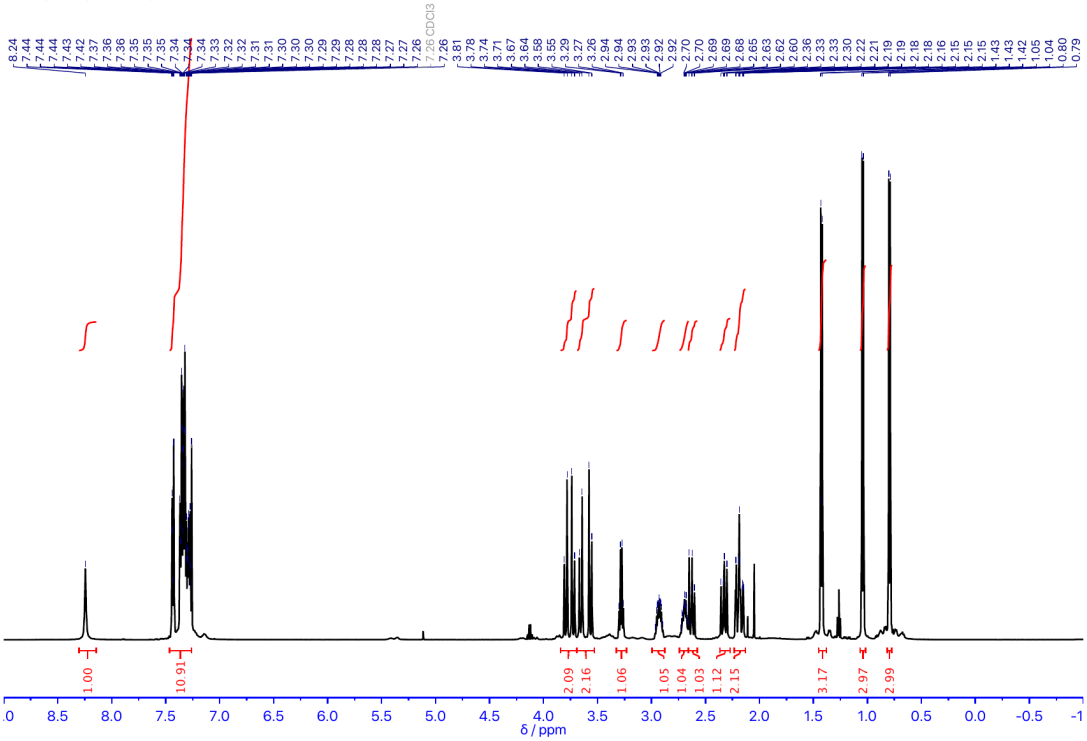


DMSO-d6, 298K, 101 MHz, 13C

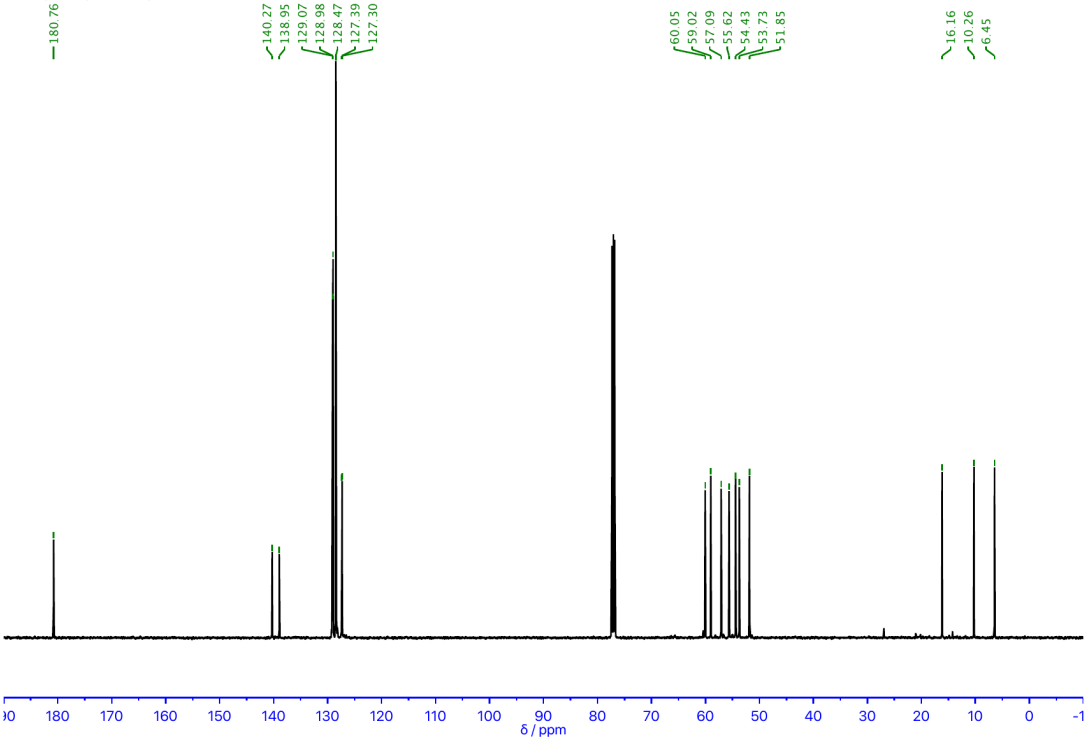


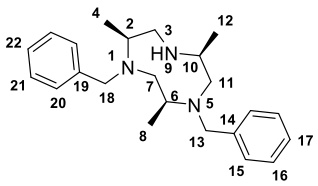


CDCl3, 298K, 500 MHz, 1H

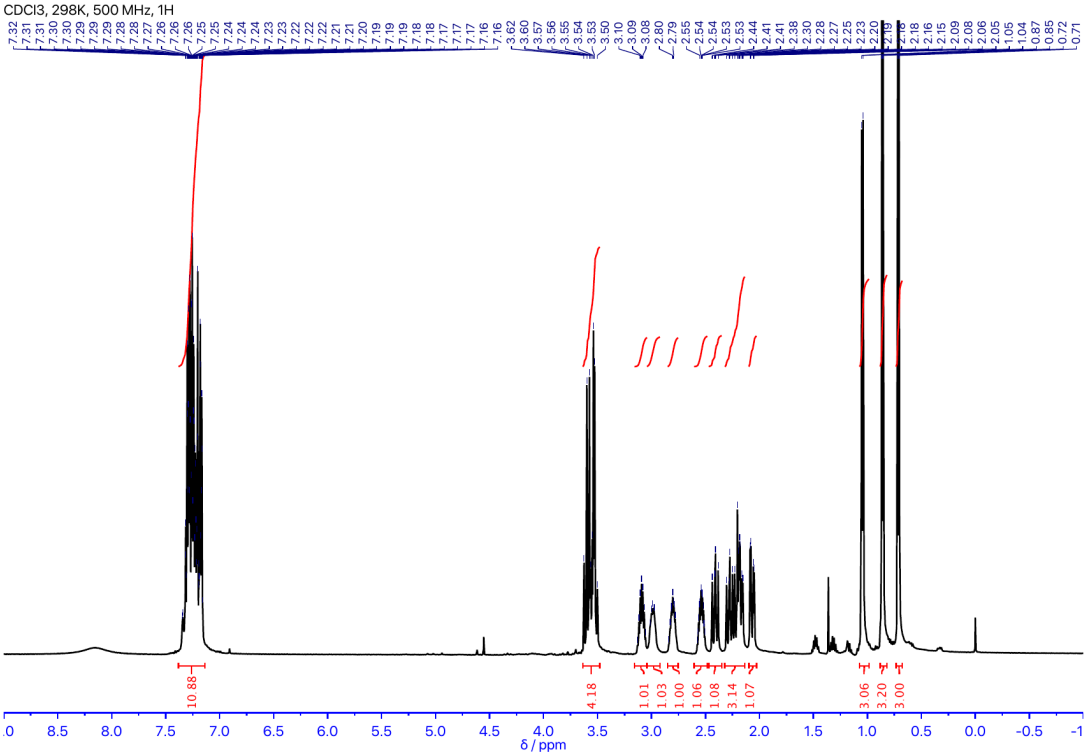


CDCl3, 298K, 126 MHz, 13C

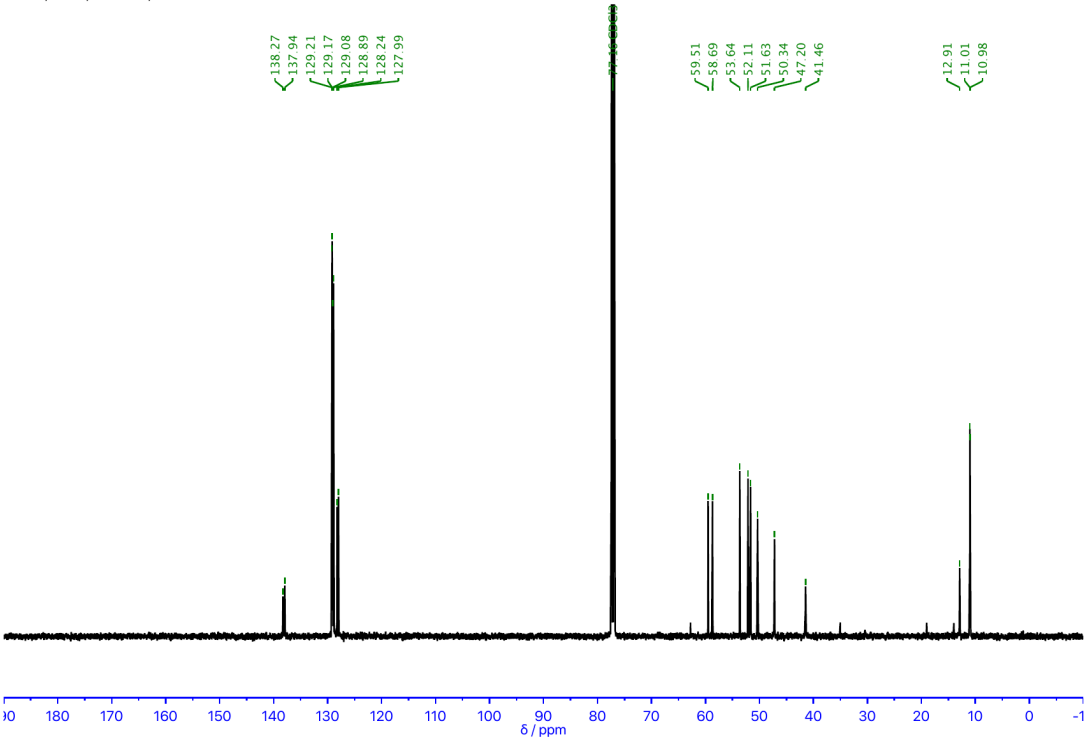


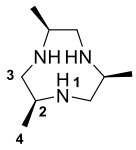


CDCl3, 298K, 500 MHz, 1H

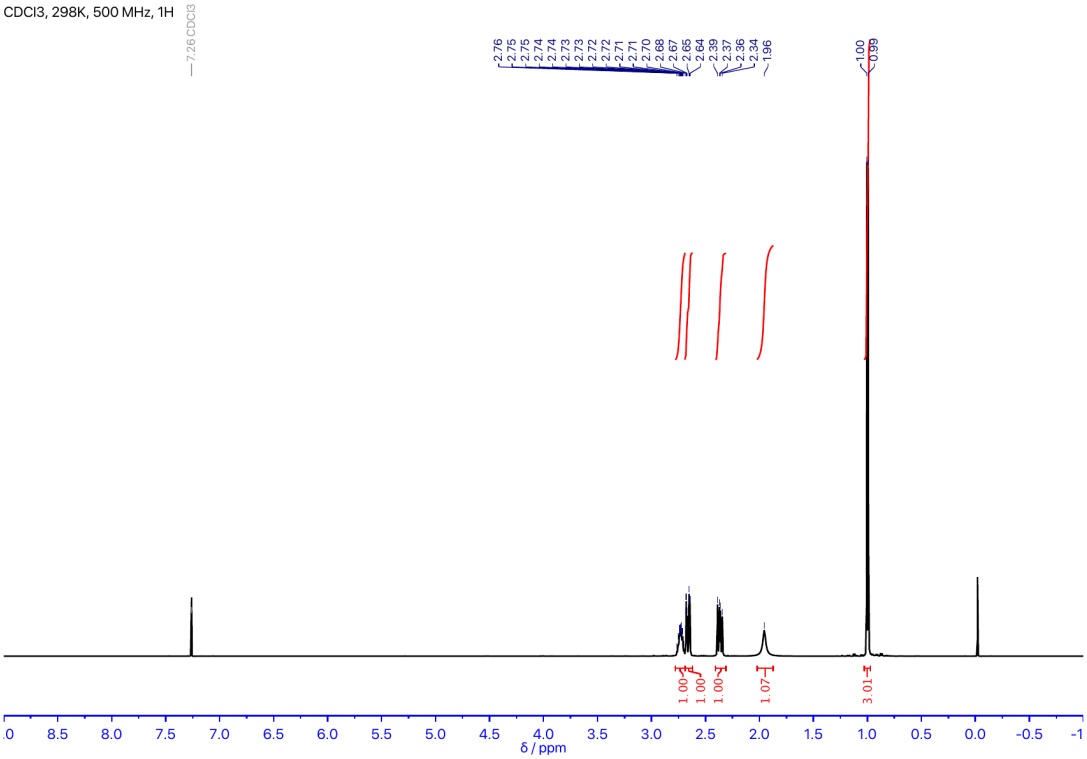


CDCl3, 298K, 126 MHz, 13C

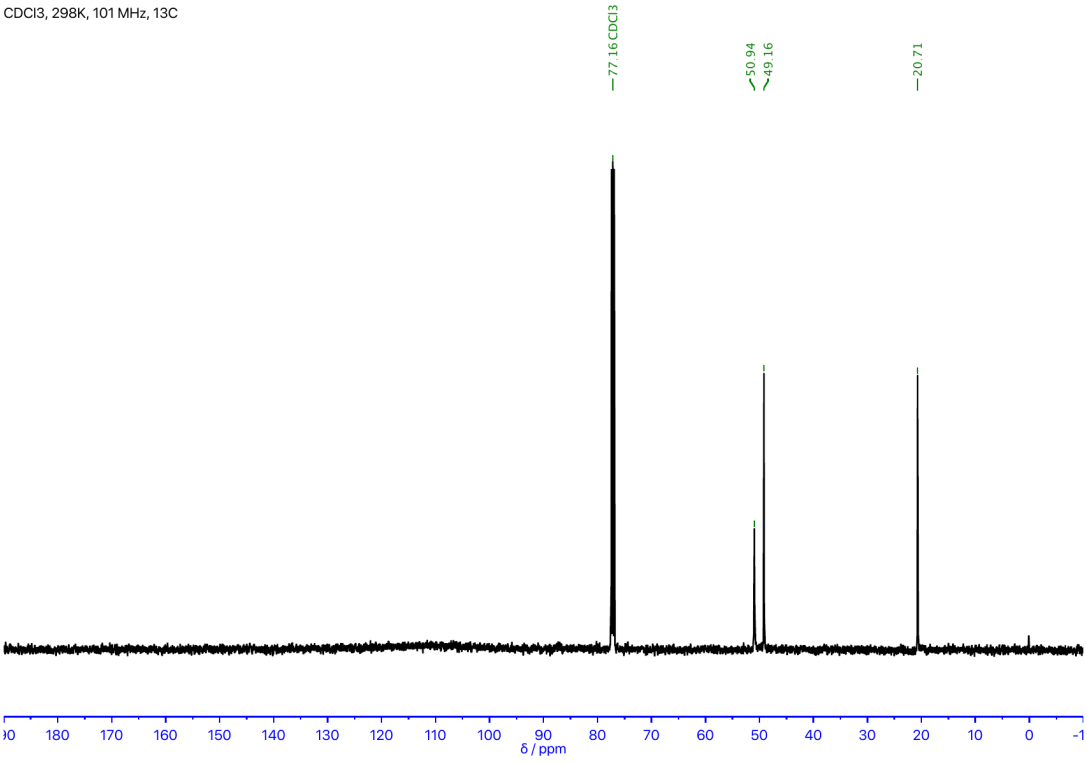




CDCl3, 298K, 500 MHz, 1H



CDCl3, 298K, 101 MHz, 13C



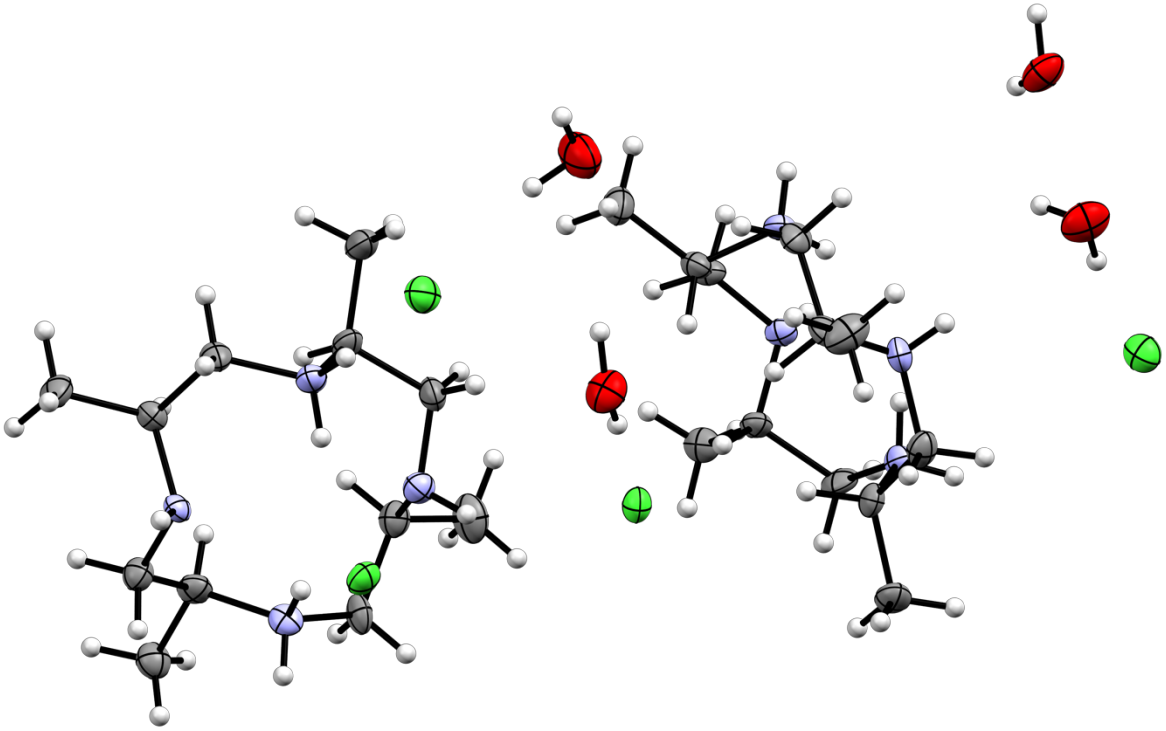


Figure S1: X-ray structure of M4-cyclen · 2 HCl · 2 H_2O (CCDC 1886728).

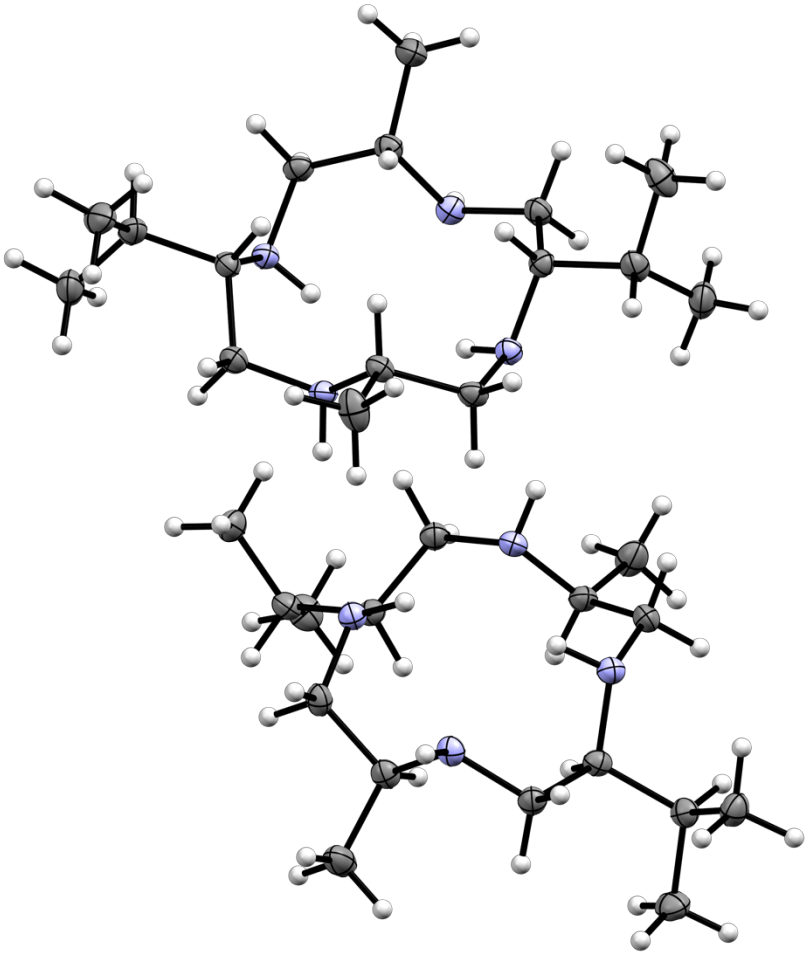


Figure S2: X-ray structure of M2P2-cyclen (CCDC 1886729).

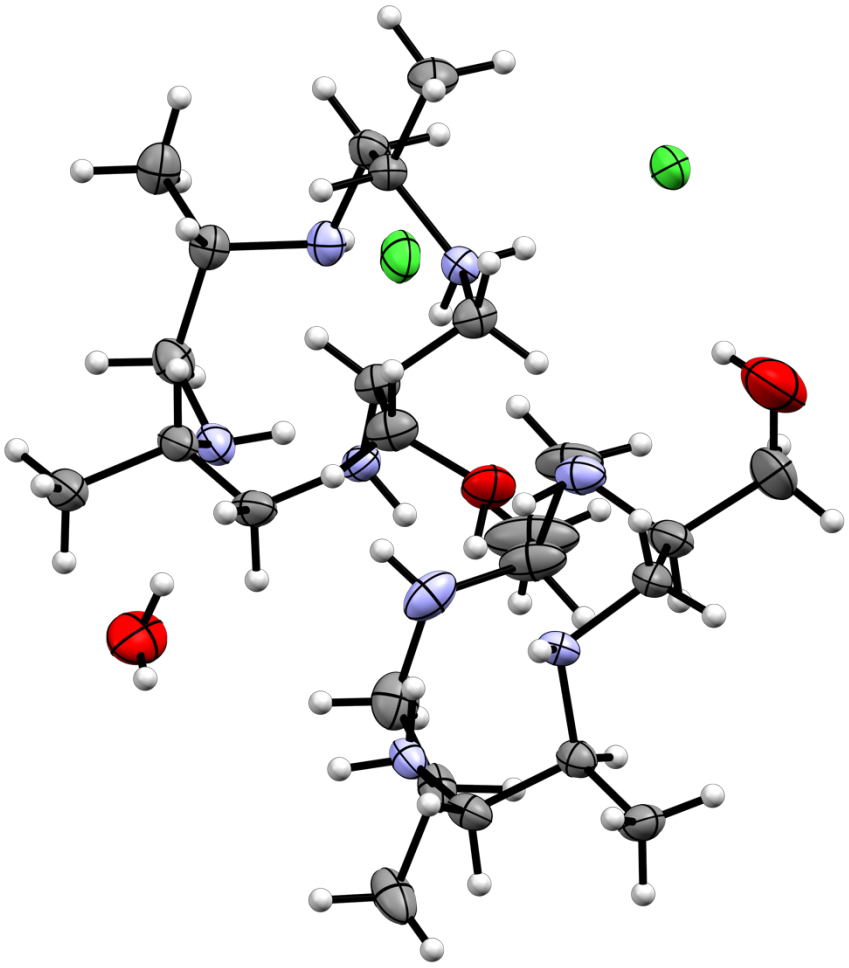
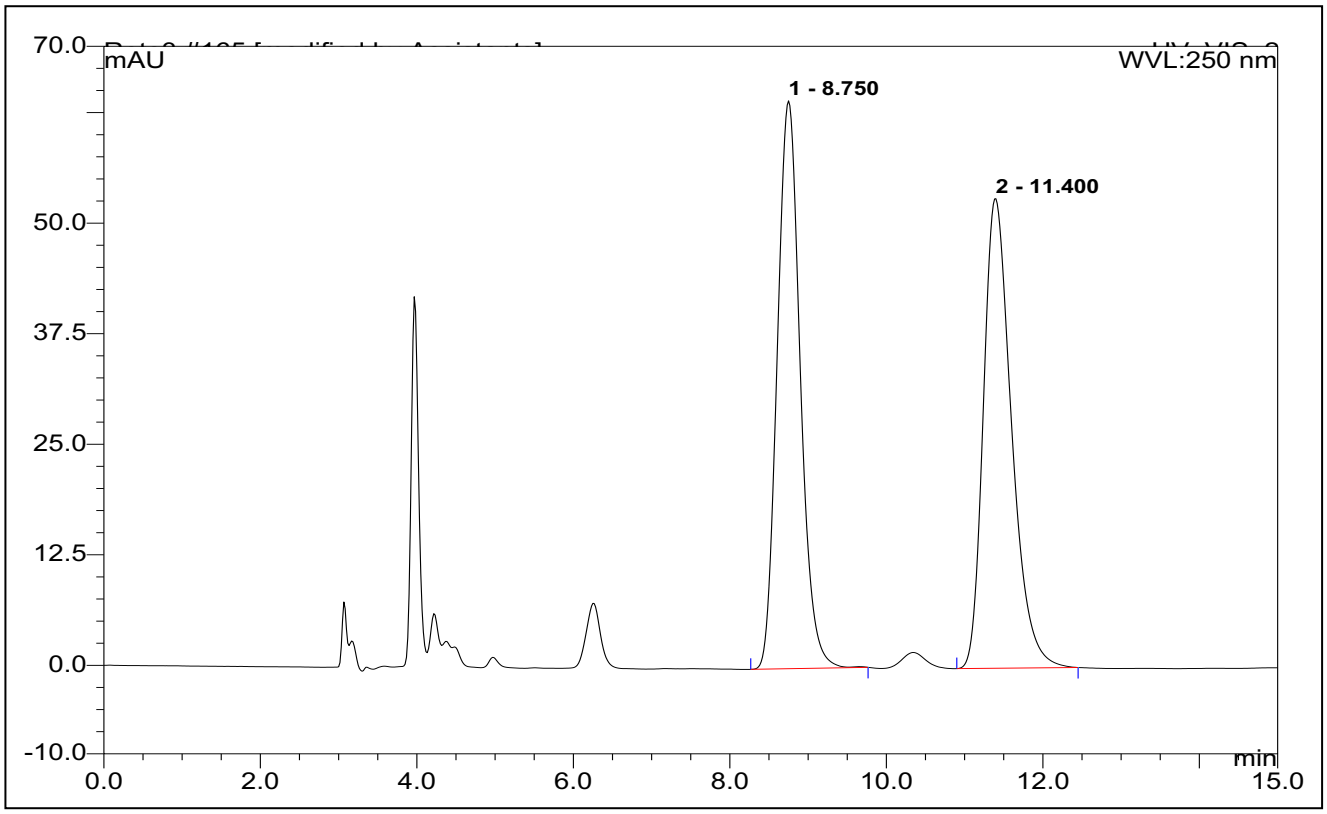


Figure S3: X-ray structure of M3O1-cyclen · HCl · 0.5 H_2O (CCDC 1886730).

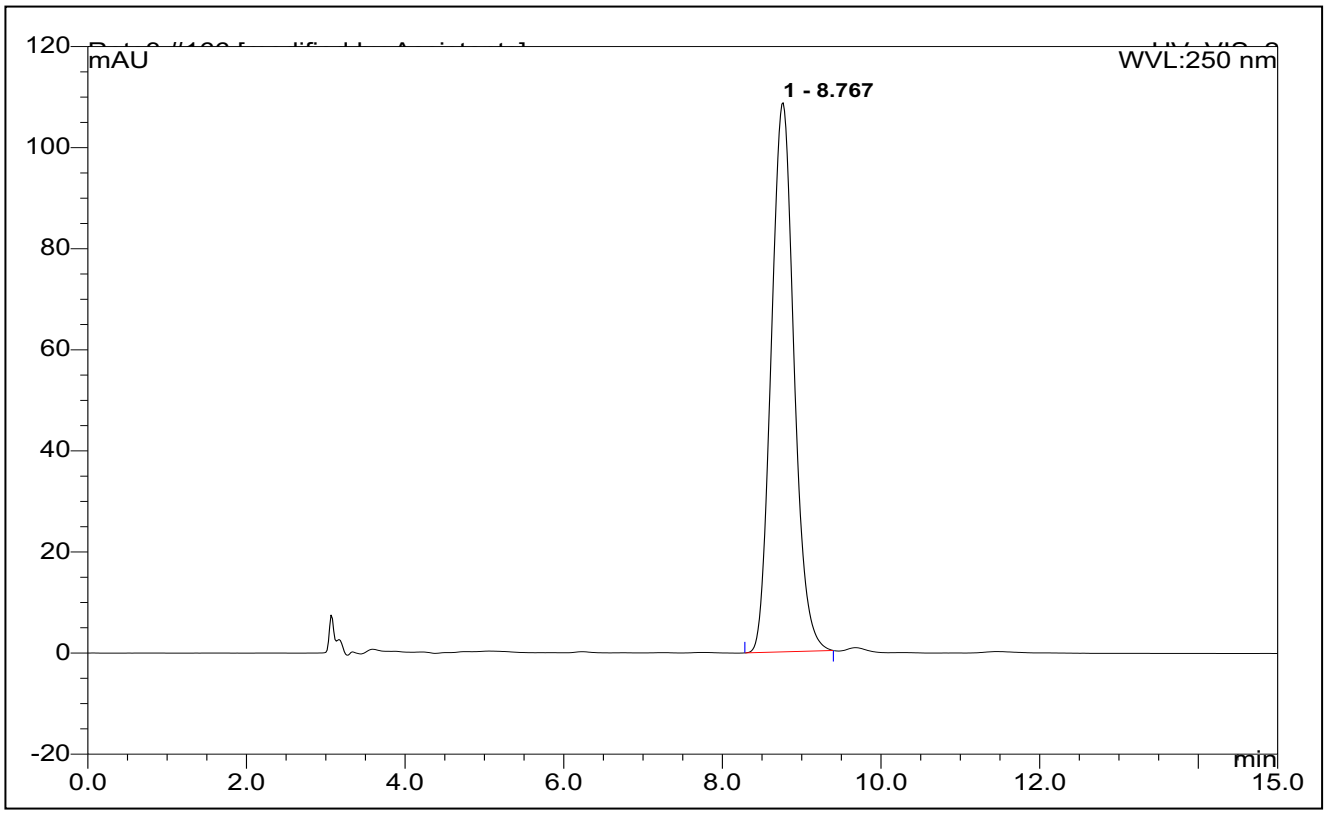
Determination of the enantiomeric ratio for aldehyde 3

The enantiomeric excess of aldehyde **3** could not be determined directly and was determined by reducing a small sample of the product to the corresponding amino alcohol.



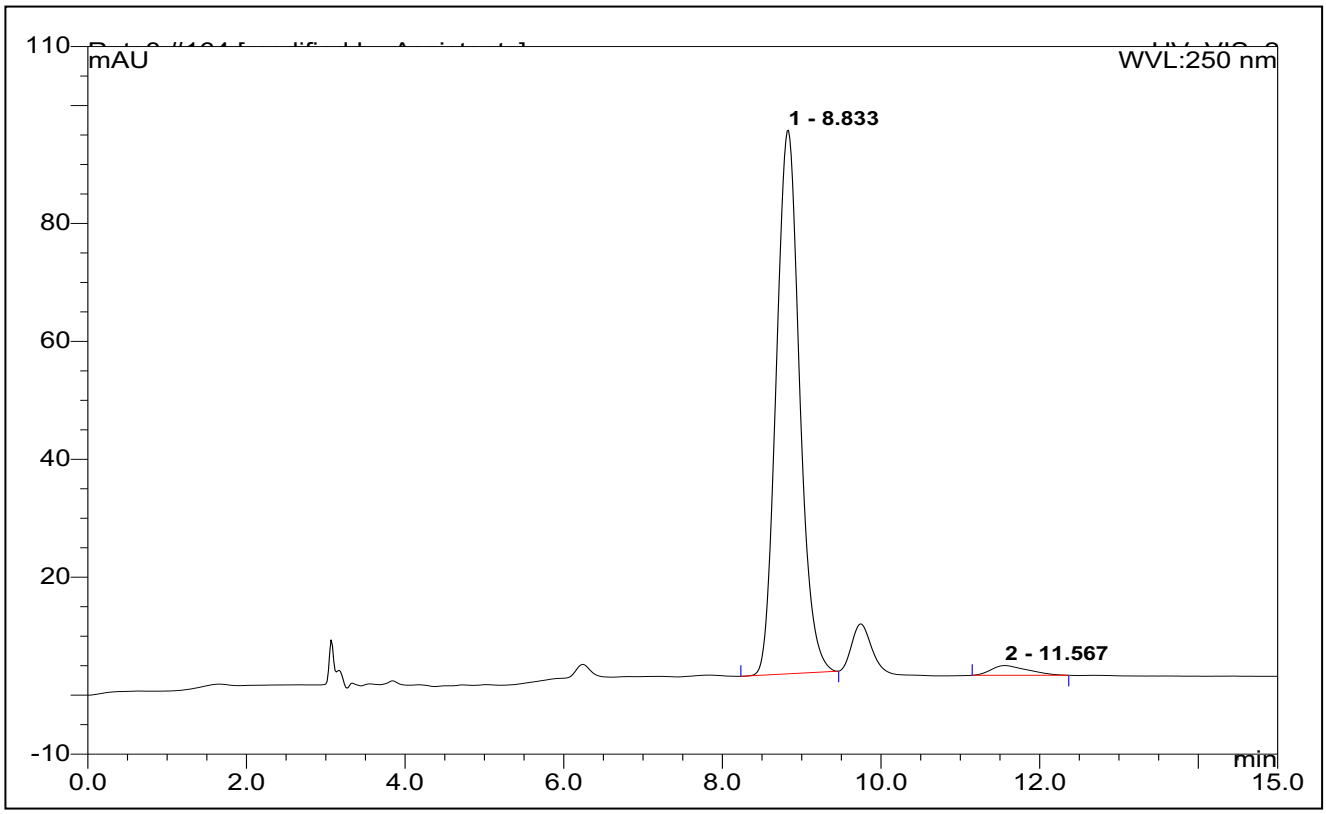
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%	n.a.	
1	8.75	n.a.	64.211	21.865	49.70	n.a.	BMB*
2	11.40	n.a.	53.097	22.131	50.30	n.a.	BMB*
To-tal:			117.308	43.996	100.00	0.000	

Figure S4: Chromatogram of racemic **1.**



No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%	n.a.	
1	8.77	n.a.	108.674	36.128	100.00	n.a.	BMB*
To-tal:			108.674	36.128	100.00	0.000	

Figure S5: Chromatogram of a reduced sample of compound **3** using the oxidation procedure described**.**



No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%	n.a.	
1	8.83	n.a.	92.201	31.399	97.28	n.a.	BMB*
2	11.57	n.a.	1.656	0.877	2.72	n.a.	BMB*
To-tal:			93.857	32.276	100.00	0.000	

Figure S6: Chromatogram of a reduced sample of compound **3** after prolonged oxidation overnight.

Determination of the diastereomeric ratio of dimer 6 by ^{1}H-NMR in $CDCl_3$

We synthesized the undesired *(R)(S)* diastereomer of compound **6** starting from commercially available (*R*)-Benzyl(1-hydroxypropan-2-yl)carbamate using the same procedures as described for the *(S)(S)* diastereomer. The *(R)(S)* diastereomer is a crystalline solid and was further purified by crystallization (cyclohexane / ethyl acetate). The diastereomeric ratio (92:8) can be determined by integration of two suitable methyl signals (see Figure below).

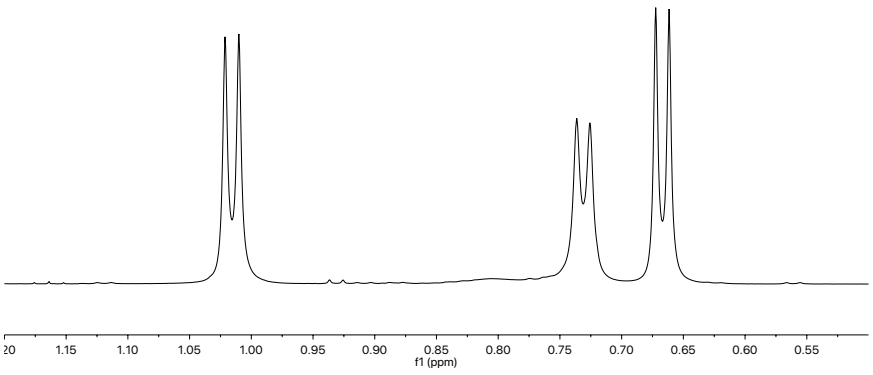
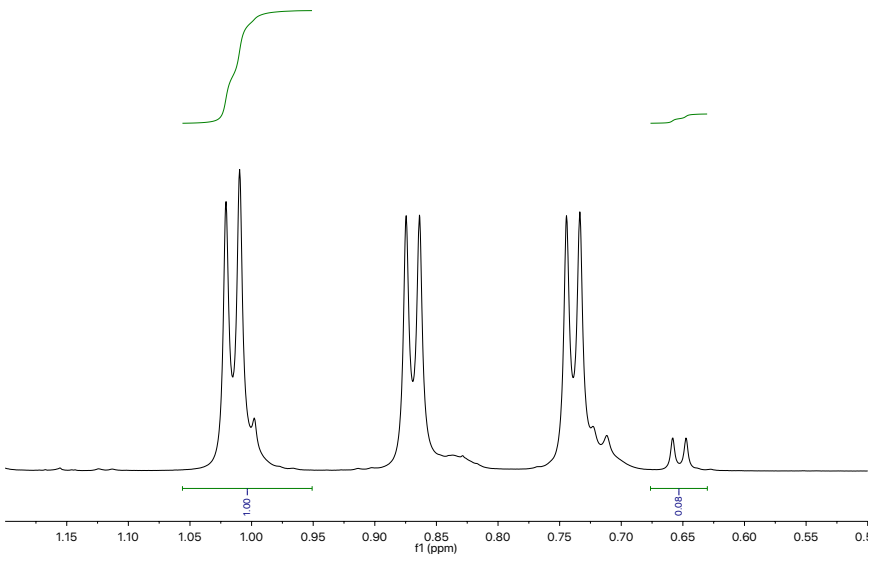
Methyl region of crystallized *(R)(S)* diastereomer	
Methyl region of synthesized dimer **6**	

Figure S7: Determination of diastereomeric ratio of compound **6** by ^{1}H-NMR.

Determination of the diastereomeric ratio of dimer 23 by ^{1}H-NMR in $CDCl_3$

Starting from commercially available *DL*-alaninol we synthesized a 50/50 mixture of both diastereomers (*RS* / *SS*). Comparison of the aliphatic region between 4 ppm and 2.4 ppm confirms the absence of the *RS* diastereomer (see Figure below).

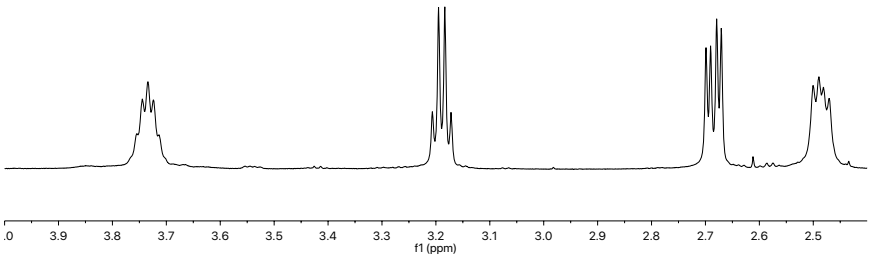
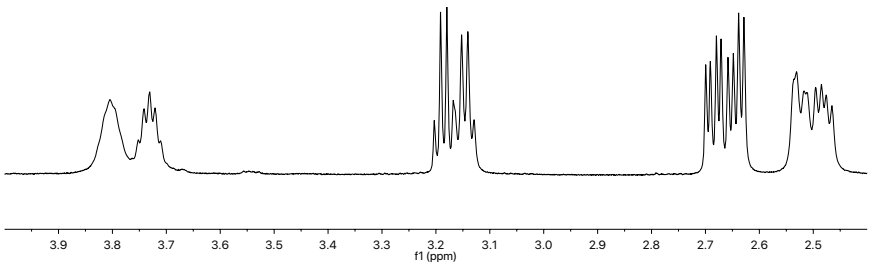
Aliphatic region of dimer **23**	
Aliphatic region of dimer **23** (50%) + 50% of wrong diasteromer	

Figure S8: Comparison of the aliphatic region for dimer **23**.